



Neuropharmacology of brain-stimulation-evoked aggression

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Abstract

Evidence is reviewed concerning the brain areas and neurotransmitters involved in aggressive behavior in the cat and rodent. In the cat, two distinct neural circuits involving the hypothalamus and PAG subserve two different kinds of aggression: defensive rage and predatory (quiet-biting) attack. The roles played by the neurotransmitters serotonin, GABA, glutamate, opioids, cholecystokinin, substance P, norepinephrine, dopamine, and acetylcholine in the modulation and expression of aggression are discussed. For the rat, a single area, largely coincident with the intermediate hypothalamic area, is crucial for the expression of attack; variations in the rat attack response in natural settings are due largely to environmental variables. Experimental evidence emphasizing the roles of serotonin and GABA in modulating hypothalamically evoked attack in the rat is discussed. It is concluded that significant progress has been made concerning our knowledge of the circuitry underlying the neural basis of aggression. Although new and important insights have been made concerning neurotransmitter regulation of aggressive behavior, wide gaps in our knowledge remain. © 1999 Elsevier Science Ltd. All rights reserved.

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Over the past three decades, a number of investigators have electrically stimulated discrete brain areas in order to evoke aggressive behavior in several species, mostly in cats and rats [12, 25, 34, 56, 75, 76, 98, 115, 119, 120]. Such models of aggression possess three particular strengths. First, the responses closely resemble those that occur under natural conditions, particularly in the cat [126]. Second, the responses can be repeatedly elicited over many trials in a reliable manner, with stable latencies and thresholds. Third, because the responses are stable, an objective standard is provided by which changes in response can be evaluated by statistical analyses. Thus, one can detect subtle response changes that occur due to the infusion of drugs, either systemically or centrally, or due to other physiological or environmental manipulations. This allows investigators to characterize the neural circuits that produce aggression. The present review describes the behavioral and neural properties of these models of aggression and surveys the literature concerning the roles of different putative neurotransmitter systems in the regulation of aggression.

In both cats and rats, aggression can be elicited by electrical stimulation of the hypothalamus and periaqueductal gray (PAG) of the midbrain, suggesting that aggression derives from similar neural substrates in both species [119, 120, 147, 206, 207]. However, the responses in rats differ greatly from those in cats, in terms of the form of behavioral responses, specificity of the neural substrate, roles of specific neural structures (e.g. the PAG), involvement of neuroactive substances (e.g. serotonin and opioids), and presumed function of the responses. Some of these disparities may result from methodological limitations: since the cat has a larger brain and the dorsal surface of its skull is larger and sturdier than the rat's, complicated techniques frequently used in cats—such as infusing drugs into a brain site and then electrically stimulating that site or another site—are only gradually becoming available for use in rats. By applying such techniques to the rat, some of the apparent differences probably will disappear. However, since the cat and rat occupy different ecological niches—the cat is a solitary, specialized carnivore, and the rat is a colony-dwelling, opportunistic omnivore—it is to be expected that different mechanisms have evolved to control aggression. By identifying the similarities and differences

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between these species in which aggression subserves different social and ecological functions, it is hoped that the principles underlying the neural control of mammalian aggressive behavior will be elucidated.

1. Behavioral aspects of brain-stimulation elicited attack in cat and rat

1.1. Categorization and measurement of aggression

There is a semantic difference between cat and rat models of aggression. In the cat, one can categorize stimulation-induced aggression as affective defense or predatory attack. In the rat, two types of motivational state in aggressive behavior, “offense” and “defense”, have been postulated as categories [40, 112, 116, 218, 222]. These categories in rat and cat are based on different criteria. Affective defense or defensive rage in the cat consists of threat postures, which may be followed by strikes upon provocation, similar to the natural defensive behavior of a cat towards intruders in a territory or towards other threats to itself or its offspring; this behavior resembles both “offense” and “defense” in the rat. However, in the rat, threat behavior (lateral threat), which is mainly displayed by the resident in territorial fighting (except in the few cases in which it is exhibited by the intruder instead), is labeled “offensive” behavior in contrast to the “defensive” attack behavior of a weaker intruder reacting to attacks by other rats [38–41]. Thus, threat in defense of a territory in the cat has acquired the label “defensive”, whereas in the rat it has generally acquired the label “offensive”.

In the cat, the distinction between defense and predation has been corroborated by neuroanatomical and pharmacological findings [36, 55, 92, 93, 184, 197]. In contrast, in the rat the distinction between “offense” and “defense” has been made on the basis of a rather confusing mixture of causation, function, form and the effect on the target of the attack, not on the basis of neuroanatomical findings; this distinction is not useful in understanding brain-stimulation-induced aggression. For the ethological point of view, see Ref. [218] for an excellent discussion of the problems caused by such an approach. Recent evidence suggests that in the rat, the neural substrate for stimulation-elicited aggression is a single, multipurpose mechanism, releasing attack whenever it is useful for survival, and that a single area, the hypothalamic aggressive area (HAA), underlies both “offensive” and “defensive” aggression, the differences between them being due to differences in environmental variables (see below). We will refrain from attributing observations of behavior to “motivational” systems implicated by observations in natural settings, and we will retain the straightforward nomenclature of the cat literature.

It should be noted that the two principal dependent variables used in these studies of aggression are: (1) *response threshold*, defined either as the lowest electrical current

delivered to the attack site that can elicit the response, or alternatively as the current intensity eliciting the response in 50% of the trials; (2) *response latency*, defined as the time between onset of electrical stimulation and elicitation of the response at a fixed current level.

1.2. Using response patterns to categorize aggression

In ethology, both the releasing and directing stimuli and the specific spatio-temporal pattern of a behavior are used to assess the “motivational state” of animals in natural settings. It has been argued [112, 116] that since such “motivational states” are constructs derived from behavioral observations, they may not have a simple relationship to the activity of a specific brain mechanism. Therefore, there is a risk in classifying behaviors obtained by electrical stimulation of a specific area into such “motivational systems”. It is evident that the response pattern under natural conditions will be affected by other controlling mechanisms in addition to the one activated by stimulation. Therefore, it is essential to assess the factors (goal-object, stimulation intensity, behavior of the opponent) that determine the spatio-temporal pattern of brain-stimulation-induced aggression. This issue is not without theoretical impact. Many of the behavioral concepts currently used in psychiatry and ethology are derived from the early influential observations on brain-stimulation-evoked behavior in cats [96] and domestic fowl [225], made at a time when the disciplines of physiology and ethology were closer.

1.3. Attack patterns in two feline models of aggression elicited by electrical or chemical stimulation

1.3.1. Quiet biting attack behavior

Quiet biting attack behavior, which is predatory in nature, is typically characterized by “stalking” of a prey object such as an anesthetized rat, followed by the biting of the back of its neck. The attack begins after onset of stimulation and usually persists until stimulation is terminated. On occasion, the cat may also strike the rat with its forepaw prior to biting it [74, 227]. This behavior is remarkably similar to the response that occurs under natural conditions where stalking and killing of a rat in the open field is readily observed [126]. Predatory attack is defined as occurring when the cat bites the target.

1.3.2. Defensive rage behavior

This form of aggressive behavior, originally described as “*affektive abwehr*” by Hess and Brugger [96], is characterized by noticeable affective signs, including piloerection, retraction of the ears, arching of the back, marked pupillary dilatation, vocalization and unsheathing of the claws. The dependent variable often measured by experimenters is the time between stimulation onset and onset of the audible portion of the hiss response. This response typically involves mouth opening, baring of the teeth, an upward curling of the edges of the tongue, and then a hiss.

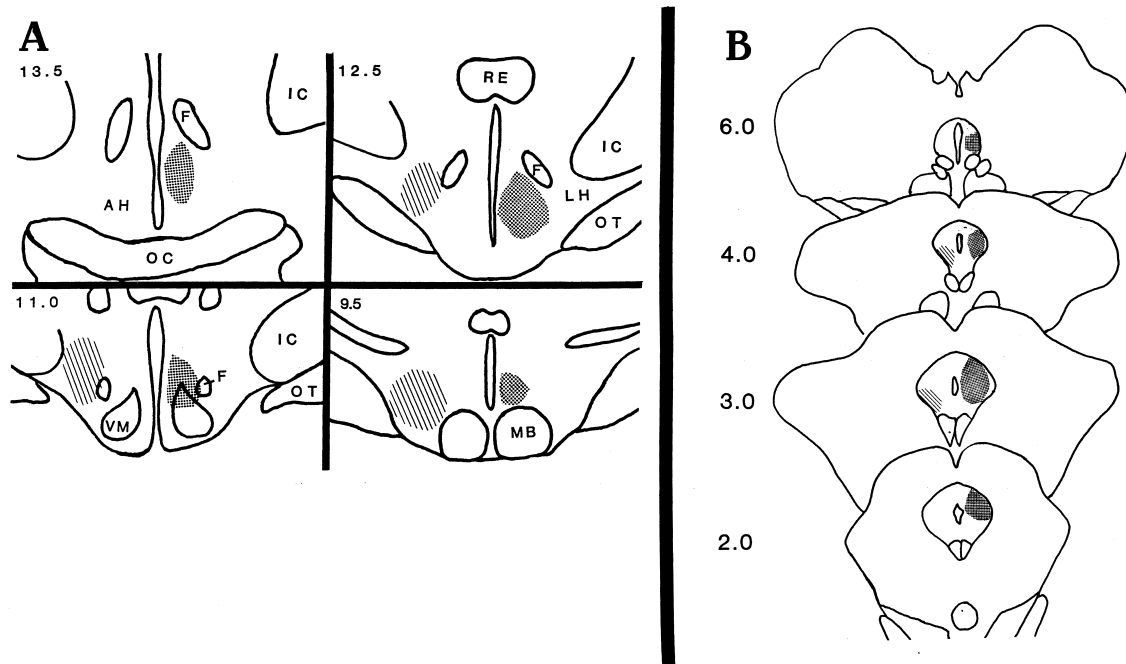


Fig. 1. (A) Distribution of sites within the preopticohypothalamus from which defensive rage (stippled area) and quiet biting attack (striped area) are most frequently elicited by electrical stimulation. Number in upper left-hand corner of figure indicates the frontal plane of section. (B) Distribution of sites within the PAG from which defensive rage and predatory attack can also be elicited by electrical or chemical stimulation. Note that, at the level of the hypothalamus, predatory attack sites are situated lateral to those associated with defensive rage and, at the level of the PAG, defensive rage sites are situated dorsal to predatory attack sites. Abbreviations: AH, anterior hypothalamus; F, fornix; IC, internal capsule; LH, lateral hypothalamus; MB, mammillary bodies; OT, optic tract; RE, nucleus reuniens; VM, ventromedial nucleus. (From Ref. [201] with permission.)

Stimulation applied at medial hypothalamic sites from which defensive rage can be elicited results in a dramatic activation of both sympatho-adrenal and cardiovascular systems, producing marked increases in heart rate, blood pressure, and peripheral epinephrine and norepinephrine levels [210].

Following its original description, this response was given the misnomer ‘sham rage’ because it was viewed as a pure motor act devoid of forebrain involvement [140]. We now know that the forebrain is typically involved: defensive rage responses can be directed at specific moving objects such as an awake rat, cat, or even the hand of an experimenter. This response is a very real one, and it has ethological significance: a nearly identical response can be evoked under natural conditions [126]. For example, this response may occur when a cat is intimidated by a threatening stimulus, when a cat perceives that her kittens are endangered by another animal, or when a cat’s territory is invaded. The typical sites from which predatory attack and defensive rage can be elicited by electrical stimulation are shown in Fig. 1.

1.4. Hypothalamic aggression in the rat: a different emphasis

Different emphases are evident in the literature on feline and rodent aggression. In cats, emphasis has been placed on intensive study of the anatomy and behavioral

pharmacology of narrowly circumscribed brain areas. In contrast, in rats, a more broad, general picture arises from studies involving either infusion of a chemical into the brain, with subsequent observation of the behavioral outcome, or peripheral administration of the substance, followed by measurement of its effects on hypothalamic attack. For example, recent work in stimulation-induced aggression in the cat focused upon the roles of opioid and excitatory amino acid receptors within the PAG. Such studies have not been carried out in the rat for two reasons. First, the cat is, at present, better suited than the rat for multiple brain manipulations. Second, in the rat the nonspecific opioid antagonist naloxone does not affect stimulation-induced attacks [112], and selective lesions of the PAG only slightly and transiently affect hypothalamic and territorial aggression [148]. Instead, in rats attention has been paid to the role of serotonin receptors in the study of the effects of ‘serenic’ drugs [112, 118, 157, 158, 219], as well as GABA, glutamate, and several other neurotransmitters, as shown in Table 2.

1.4.1. Continuous diversity of hypothalamic attack patterns

Attacks elicited by hypothalamic stimulation in the rat have been classified into ‘complete’ and ‘incomplete’ attacks [108], and into ‘affective’ and ‘quiet attacks’ [161–163], ‘jump attacks’, ‘bite attacks’ [231], ‘attack jumps’, and ‘clinch fights’ [117, 120, 219]. Such distinctions are necessary to describe the diversity of the attacks,

but the typology actually covers a continuum of forms, with many intermediate forms and transitions between them.

There is a general pattern in all attacks. Attack patterns range in violence from mild biting of the neck of an opponent through hard biting of the head and back, through hard biting of the back accompanied by hind paw kicks in the flank, to clinch fights and attack jumps [115, 117, 119]. The bite is always present and the front paws may be placed at the opponent's neck or back as a concomitant for biting. Subsequently, the hind paws may come into action to kick the flank, chest or belly of the adversary. Attack jumps arise when the opponent goes into an upright position, presumably to protect its back from being bitten. In attack jumps, the attacker jumps from some distance toward the opponent, using its hind paws for takeoff and tail for balance and support. Upon landing, the attacker tries to bite the head, while delivering a forceful blow with the hind paws against the opponent's chest or belly. In clinch-fights, the rats often become locked in an on-top/on-back position. Clinch-fights occur when one of the rats loses its footing following an attack jump, or when an opponent fails to assume an upright defensive position. From bite attack to clinch fight and attack jump, there is a general tendency to increase the arching of the back. The head and neck are the first targets of attack followed by the upper and lower back [115, 117, 147, 149]. Although a dominant rat could easily bite the exposed ventral surface of a submissive rat lying on its back, this surface is rarely bitten, even in a clinch fight [117]. Rats fighting in natural settings bite the same targets [38–41, 149].

Hypothalamic attack can be directed against subordinate rats, dominant rats [108, 117], anesthetized rats, dead-and-frozen rats [117] and mice [12, 105, 108, 161–163, 223, 231]. Male rats also attack receptive or unreceptive females [108, 117, 173]. Female rats attack other females as well as males [114, 149]. In the absence of a rat-like object, attack does not occur. For example, rubber toys shaped like rats are not attacked [117]. Such findings parallel the patterns observed in the cat, where stimulation-induced attack is preferentially directed against live rats (as opposed to dead or toy animals) [125].

Different strains of rats have different hypothalamic attack patterns. For example, in the beige inbred CPB-WEzob strain, bites on the head are the dominant pattern, whereas in random-bred albino Wistar CPB-WE rats, the dominant pattern is a bite directed at the back, a pattern which is absent from the inbred strain [115]. The attacks derive from the same anatomical area in both strains [115, 119, 120].

1.4.2. Three factors determining the form of hypothalamically evoked aggression in the rat

We argue that, upon stimulation of HAA in the rat, a multipurpose neural mechanism is activated that, under natural conditions, subserves attack whenever it is required

for survival. The form of the attack is determined by: (1) the intensity of stimulation current; (2) directing stimuli from the opponent; (3) the tactics the opponent adopts to avoid being attacked, e.g. hiding the attack-directing stimuli from the attacker. Curiously, the exact position of the electrode within the HAA has relatively little effect on the form of the attack [119, 120].

First, at intensities below the threshold for attack, stimulation makes the rat more self-directed and more sensitive to the activities of its partner. The partner reduces its physical interactions with the stimulated rat. As stimulation intensity increases, the withdrawal of both rats from social interactions also increases [90], but there are still no signs of aggression. At the approximate threshold intensity, the mutual withdrawal from social interactions apparently fails and violent interactions take over, as bites directed at the back and neck of the partner are released. Further increases in the intensity of stimulation will shorten the latencies for attack and bias the attacks towards more violent forms, accompanied by a tendency to use the hind paws to kick at the body, in virtually all electrode placements studied [114]. Increasing stimulation intensity seems to activate the attacker in cephalo-caudal order [113, 115, 117].

Second, strong directing stimuli on the head and rostral part of the back of the opponent are apparently essential components in shaping the form of the attack [117].

Third, the tactics of the opponent are important in determining the form of the attack, as mentioned above. Other examples include the following. If the opponent freezes in a crouched position, a bite accompanied by a kick of the hind paws often develops into a clinch fight. The treatment of opponents with a high dose of morphine in order to alleviate pain and anxiety, a procedure which is now routine, causes them to stop emitting 22 kHz ultrasonic distress vocalizations and to stop adopting defensive upright positions. Consequently, attack-jumps are abolished (Fig. 2) and only straight attacks on the back occur. If the stimulation is strong, such attacks are followed by a clinch. Neither latencies to attack nor the threshold current intensity are changed. These observations show that while the active participation of the opponent is not required to elicit an attack, the opponent's defensive tactics affect the form of the attack.

The hypothesis that these three factors allow for the observed variety in the form of fights is supported by the fact that the intensity of the attack may be diminished by decreasing stimulation intensity, treating the attacker with a drug (e.g. L-propranolol; Kruk, unpublished results), or treating the opponent with a drug such as morphine. In all these cases the proportion of clinch fights and jump-and-bite attacks decreases considerably. These findings also clarify why it is questionable to classify brain-stimulation-elicited aggression as "offensive" or "defensive" on the basis of superficial similarities with behavior expressed in natural settings.

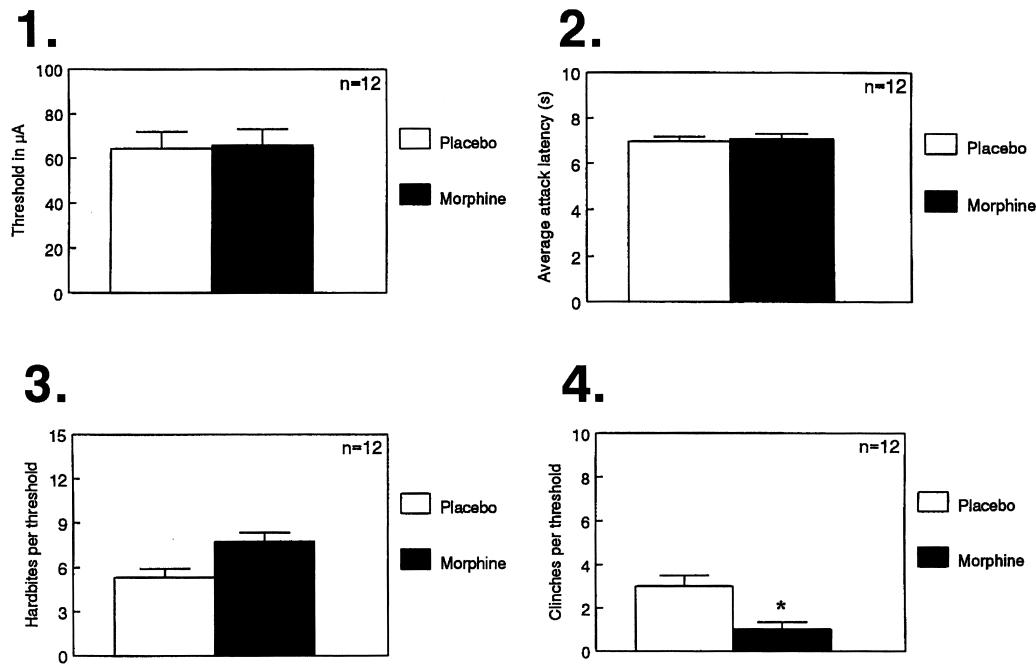


Fig. 2. Changes in the attack pattern of six rats stimulated in the HAA, during attack threshold determinations lasting 15–20 trials, as a consequence of the i.p. injection of 20 mg/kg morphine in 12 naive rats used as their opponents, compared with 12 control rats in a balanced design. Morphine injection 30 min before the start of a threshold determination completely immobilizes and anesthetizes the opponents, but does not change the latency to attack or the attack threshold in the untreated attacking rat (panels 1 and 2). However, morphinized opponents receive more hard-bites on their back (panel 3). Morphinized opponents exhibit fewer clinch fights than placebo-treated controls (panel 4). Moreover, morphinized opponents are not subject to jump-and-kick attacks, in contrast to controls (not shown).

1.4.3. Behavioral concomitants of hypothalamic attack in the rat

In contrast to earlier observations [217], it is now known that stimulation of different hypothalamic areas yields different behaviors [120–122]. Within the region from which attack can be elicited, other responses can be obtained: piloerection, teeth chattering, quiet locomotion, flight, escape, and self-stimulation. Some of these concomitant responses are more prepotent than others. For example, piloerection is an inconsistent concomitant response, which often disappears after a few stimulations. Each of these behaviors has its own typical distribution in the hypothalamus, sometimes overlapping with aggressive responses, sometimes as an independent response. Briefly, the anatomical distribution of teeth chattering sites closely matches that of attack sites, whereas flight and locomotion sites may be located rostrally and caudally far beyond the region where aggression can be elicited [120–123]. Teeth chattering and piloerection are more prevalent in the area medial to the fornix, whereas attack proper is more prevalent in the subfornical area, giving way to social grooming in the direction of the lateral hypothalamus. These findings suggest that in cat and rat one finds a similar diminution of “affectivity” when moving from medial to lateral through the hypothalamic area for aggression [121]. Piloerection is also a component of the defensive attack pattern obtained from the medial hypothalamus in the cat.

One concomitant response is self-stimulation. However, the ability to elicit aggression cannot be predicted from the rewarding or aversive properties of the stimulation. For example, in one study, attacks were induced from 27 of 51 electrodes aimed at sites in the HAA. In six of these sites the rats learned self-stimulation; in 11 sites they learned to switch stimulation off; in eight sites the rats learned both self-stimulation and the switch-off response, and in two sites they learned neither. From the 24 sites that did not produce attacks similar results were obtained [113]. A similar orthogonal relation between self-stimulation and the elicitation of aggression was reported by Heldon et al. [95]. Because attack can be induced at sites that produce self-stimulation, switch-off, and escape, as well as at sites that produce neither [113], it is likely that hypothalamic attack in the rat does not derive from specific hedonic, aversive or flight-inducing properties of stimulation.

When observing hypothalamic attacks in rats, one is tempted to use concomitant behaviors accompanying attack as criteria to classify the attacks into motivational categories such as “predatory”, “fear-induced”, “irritation-induced”, “offensive”, “defensive” or “territorial” aggression [151]. However, since the neural substrates for several different neural systems are near to, or overlapping, one another within the hypothalamus, stimulation may activate several systems and thus produce a “mixed” combination of responses. Therefore, in the rat it can be unclear

whether the responses elicited by stimulation arise from one neural system or overlapping systems [172]. It is possible that several of these concomitant responses form the overall characteristic pattern of hypothalamically elicited attack behavior. Therefore, one cannot use concomitant responses to classify hypothalamic attack into motivational categories. However, such responses can serve as useful controls for behavioral specificity of drug effects [112, 118, 158, 219].

1.4.4. Hypothalamic attack and “natural” aggression

Rat aggression has been studied extensively in experimental paradigms where brain stimulation was not employed. The attacks which occur in naturalistic paradigms (such as in maternal aggression, offensive or defensive territorial aggression, mouse-killing, and in the “cornered rat” paradigm) and in artificial paradigms (such as shock-induced fighting) all share similarities with hypothalamic attack. For example, the attack patterns and targets are similar. However, these attacks also differ from hypothalamic attack. Shock-induced fighting, for example, is a purely defensive, reflexive response to a painful stimulus [38–41]. It resembles the defensive response of an attacked opponent in the upright position, but lacks the purposeful, active approach and goal-directedness of hypothalamic attack. For a further comparison of hypothalamic aggression to aggression in other settings see Ref. [112]. Such comparisons have led to the conclusion that hypothalamic attack in the rat is the consummatory response, or end-point behavior of the agonistic repertoire and, as such, constitutes a category in its own right. It reflects the behavioral expression of a brain mechanism that is activated when control over the behavior of another organism is lost, and agonistic strategies such as threats, displays and warnings are insufficient to reinstate control. Under such conditions, inhibition over an attack–release mechanism that can be activated from the hypothalamus is overridden and a well-directed attack results. According to this concept, it is no surprise that the attack patterns observed during hypothalamic stimulation can also be observed in territorial settings and resident–intruder paradigms, in maternal aggression and in the cornered rat paradigm. Studies of feline hypothalamic attack addressing the details of effector mechanisms, modulatory mechanisms, and the specific sensory and endocrine changes involved, support this view of the function of hypothalamic attack in natural settings [22, 73, 76, 206, 210, 211].

It is not likely that hypothalamic stimulation brings the rat into a “motivational state of aggression” in the classical sense of the word [116, 128]. The effects of hypothalamic stimulation are quick to appear, and they disappear quickly after stimulation is terminated; also, “lateral threat” is absent from these attacks. Some of the attacked targets differ greatly from the targets attacked in natural agonistic settings. Stimulation seems to elicit unplanned fighting which is out of context from the functional point of view. These behavioral observations suggest that hypothalamic

attack in the rat is the expression of a general-purpose attack mechanism used in all kinds of settings, regardless of their “motivational” nature. In natural settings, attacks probably are released when modulatory brain mechanisms (e.g. medial amygdala, the prefrontal cortex, the septum or PAG) are suppressed. Indeed, stimulation of HAA apparently overrides or bypasses those inhibitory mechanisms [112, 200, 201]. The mechanism that releases attack presumably is not confined to the hypothalamus, but includes such other regions as the PAG, medial amygdala, lateral septum, and the ventral output pathways descending caudally to the brain stem in the cat [201, 206] and rat [173, 175] in different degrees depending on the setting in which aggressive responses are functionally required.

2. Central pathways mediating attack behavior

In attempting to understand the neural substrates of aggression, two concepts and some definitions should first be noted. First, a crucial distinction must be made between two classes of neural structures. The first class of structures produces the *expression* of an attack response when stimulated. These structures, and the pathways arising from them, *mediate*, or carry the neural signals necessary for, the motor and autonomic aspects of aggression. Sites within these structures are termed, for example, “defensive rage sites” or “predatory attack sites”. The second class comprises limbic structures whose stimulation does not produce the expression of an attack response; rather, stimulation of these structures increases or decreases thresholds (“suppresses” or “facilitates” the behavior respectively) for responses elicited by concomitant stimulation of an attack site. In other words, these structures *modulate*, or “mediate the modulatory effects on” aggression, and are termed “modulatory sites”. For example, “medial amygdaloid facilitation of PAG-elicited defensive rage” is shorthand for “a decrease in the threshold for defensive rage behavior elicited by electrical stimulation of the PAG, which occurs as a result of electrical stimulation of the medial amygdala”. Second, while in the cat, the pathways mediating predatory attack and defensive rage are clearly separate, this particular separation has not yet been found in the rat, although ongoing research is beginning to map out the efferent pathways from the hypothalamic area where grooming can be elicited (hypothalamic grooming area; HGA) [176] and flight-producing sites [173], as well as HAA [173, 175]. The findings of these studies generally parallel the findings in the cat. The following discussion is based on work in the cat, referring to work in the rat when relevant.

2.1. Central pathways mediating attack behavior in the cat

In the cat, the efferents from the hypothalamus and neighboring regions of the midbrain PAG which subserve aggression were initially examined by Chi and Flynn [56, 57] and

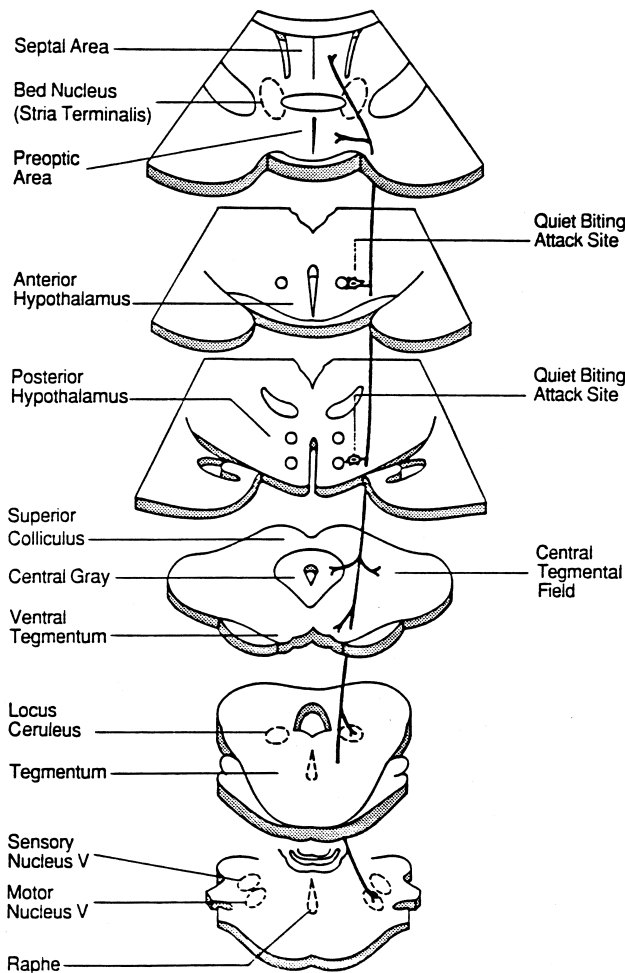


Fig. 3. Diagram indicating the principal ascending and descending projections of the perifornical lateral hypothalamus associated with quiet biting predatory attack behavior. Note the projections to the PAG, tegmental fields, locus coeruleus and motor nucleus of cranial nerve V. (From Ref. [201] with permission.)

later by others [75–77, 184]. The methods employed in these studies included traditional tract-tracing methods such as the Fink–Heimer method, tritiated amino acid autoradiography, and ^{14}C -2-deoxyglucose autoradiography, as reviewed elsewhere [201, 206].

2.1.1. Pathways mediating predatory attack behavior

Quiet biting attack sites are located along the rostro-caudal extent of the lateral hypothalamus, but the most sensitive region is the perifornical region [201, 206]. In the brainstem, attack sites are located in the ventral aspect of the PAG [184], ventral tegmentum [25] and as far caudally as the lateral tegmental fields of the pons [34]. The most important cells which give rise to ascending and descending fiber systems mediating the expression of predatory attack are situated in the perifornical lateral hypothalamus. Descending fibers from the lateral hypothalamus project to nuclei that appear to be essential for predatory attack, including the trigeminal motor nucleus, the locus coeruleus,

the ventral half of the PAG, and the ventral and lateral tegmental fields of the midbrain and pons (see Fig. 3). The monosynaptic projection to the trigeminal motor nucleus may activate jaw-opening and -closing mechanisms for the biting component of the attack response. The projection to the locus coeruleus may serve two functions. First, this nucleus projects to the intermediolateral column of the spinal cord [58, 153]; this projection would thus complete a disynaptic pathway for activation of the sympathetic nervous system, which is integral to the process of both predatory attack and defensive rage. Second, the locus coeruleus contains the largest pool of noradrenergic fibers that are distributed to the forebrain. Since the noradrenergic system facilitates defensive rage [26, 27], it is likely that these ascending fibers provide a ‘‘positive’’ feedback mechanism to the hypothalamus and limbic system. This pathway could serve as a substrate for prolongation of the attack response. Interestingly, central noradrenergic facilitation has also been proposed for aggression in the rat (reviewed in Ref. [91]). In a parallel fashion, a similar function may be served by ascending fibers associated with the perifornical hypothalamus that supply modulatory structures such as the septal area, bed nucleus of the stria terminalis (BNST) and preoptic region [49, 186, 208]. The septal area is also involved in rat aggression [175].

Because the majority of efferents from predatory attack sites in the ventral PAG and pontine tegmentum project to the lateral hypothalamus [184], it is likely that these fibers may complete an additional positive feedback loop. Descending projections from PAG predatory attack sites pass for short distances to the lateral tegmental region from which attack can be elicited [34] and to the pontine raphe complex, a region which, when stimulated, suppresses predatory attack [187]. The notion that the projection to the raphe is associated with suppression of attack receives indirect support from the observation that parachlorophenylalanine (PCPA), which blocks the rate-limiting enzyme in the biosynthesis of serotonin, facilitates the occurrence of this response [133]. Thus, it would appear that the ventral PAG modulates the activity of the perifornical hypothalamus, where the primary integration for this response takes place.

2.1.2. Pathways mediating defensive rage behavior

The primary pathways associated with defensive rage arise from the medial hypothalamus [76, 77] and dorsal PAG [184]. Remarkably, fibers arising from defensive rage sites in or near the ventromedial hypothalamus primarily pass rostrally, terminating principally upon neurons within the medial anterior hypothalamus–preoptic zone, an area from which this response could also be elicited. Inputs to this zone include axons from limbic regions such as the amygdala, septal area and BNST [48, 49, 211]. The descending fibers which innervate the PAG mostly originate from this zone (see Fig. 4). This pathway from medial hypothalamus to dorsal PAG constitutes the principal pathway for defensive rage in the cat. These findings provided

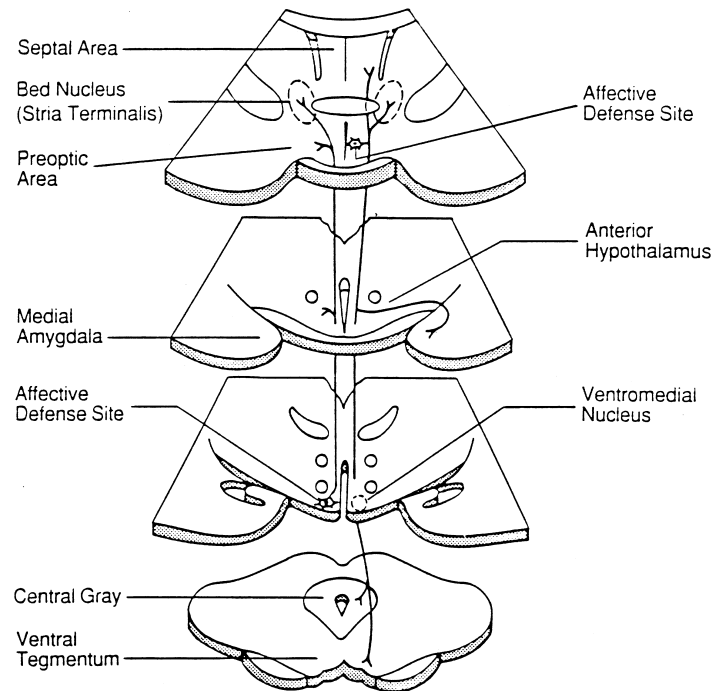


Fig. 4. Diagram indicating the principal ascending and descending projections of the medial hypothalamus associated with defensive rage behavior. Note that fibers mainly ascend from the ventromedial hypothalamus to the anteromedial hypothalamus and preoptic region and that fibers that supply the PAG arise principally from the anteromedial hypothalamus. (From Ref. [206] with permission.)

the basis for further studies, described below, concerning the role of catecholamines and excitatory amino acids in this pathway.

In contrast to the predatory attack system, the majority of fibers arising from PAG defensive rage sites pass caudally, to the locus coeruleus, sensory and motor nuclei of the trigeminal complex, and neighboring regions of the midbrain and pontine tegmentum. The projections to the locus coeruleus may serve the same two functions as noted above for the predatory attack system. Other pathways governing autonomic regulation may include fibers from the caudal PAG which appear to descend to autonomic nuclei of the lower brainstem [24]. The efferents to the trigeminal complex may mediate the vocalization that normally accompanies defensive rage. Similar to the predatory attack system, some of the fibers arising from the dorsal PAG project rostrally to portions of the medial hypothalamus that produce defensive rage, and may complete a similar positive feedback loop, allowing for the response to be prolonged. However, it should be noted that the PAG contains sites which, when stimulated, can facilitate or suppress defensive rage or predatory attack elicited by hypothalamic stimulation [165, 229]. The pathways from the PAG for predatory attack and defensive rage are summarized in Fig. 5.

2.1.3. Limbic pathways that modulate predatory attack and defensive rage

Limbic structures give rise to pathways that synapse upon hypothalamic or PAG cells and modulate aggressive

behavior [201, 202, 205]. Because little is known about the transmitters involved, we will only briefly discuss pathways from the amygdala.

Several important modulatory pathways issue from the amygdala. The most well-documented pathway, the stria terminalis, arises from the medial nucleus, medial aspects of the basal complex, and the area in and around the cortical nucleus. These fibers arise from modulatory regions which, when stimulated, facilitate defensive rage and suppress predatory attack [42, 48, 70, 211]. The primary target of these fibers is the medial hypothalamus, in which they terminate over a wide area, extending from the anterior-preoptic zone to the posterior aspect of the ventromedial nucleus [110, 211, 228]. In contrast, fibers which arise from the central nucleus, lateral aspects of the basal complex, and the lateral nucleus are distributed to the BNST and, via the ventral amygdalofugal pathway, through the medial forebrain bundle to the lateral hypothalamus, PAG, and autonomic nuclei of the caudal medulla. It has been shown that the cells of origin of these fibers are associated with suppression of defensive rage and facilitation of predatory attack [42, 48, 70]. Thus, strikingly, some cell groups in the amygdala facilitate predatory attack but suppress defensive rage and other cell groups do the opposite. It is likely that the outputs of the amygdala to the medial hypothalamus and PAG constitute direct routes by which the amygdala modulates aggressive reactions, and the output to the BNST is an indirect route. Evidence in support of this indirect route is that: (1) the BNST projects directly to the medial hypothalamus and PAG [97, 228]; (2) BNST

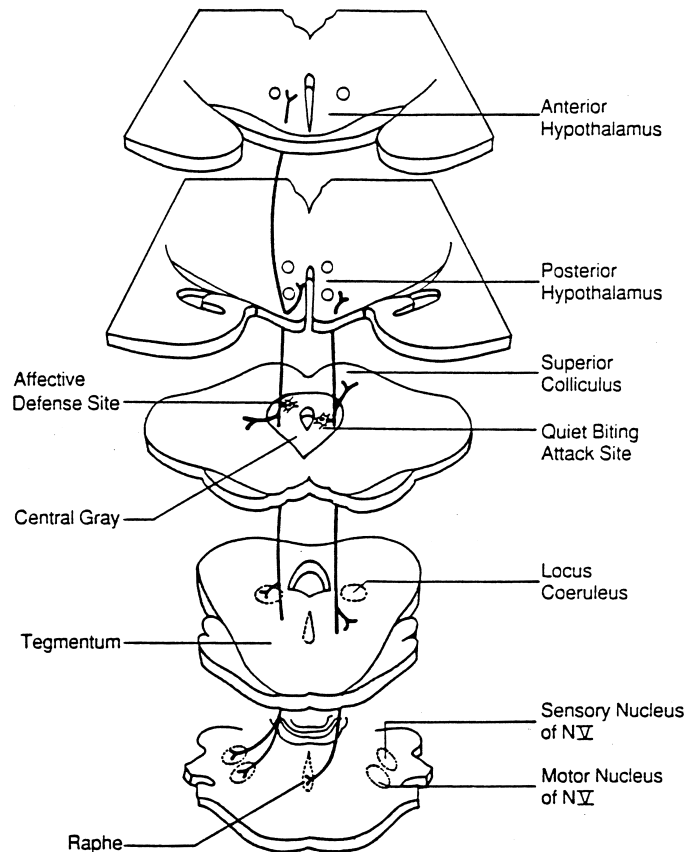


Fig. 5. Diagrams indicating the principal efferent projections from PAG sites associated with defensive rage (left side) and predatory attack (right side). Note that fibers associated with defensive rage arising from the PAG are distributed rostrally to the medial preopticohypothalamus from where this response can also be elicited and caudally to the locus coeruleus, tegmental fields and trigeminal complex. Also note that the distribution from predatory attack sites is more limited in which a primary projection ascends and synapses in the posterior lateral hypothalamus where this response can also be elicited. Descending projections supply the central tegmental fields and median raphe. (From Ref. [206] with permission.)

stimulation results in modulation of both defensive rage and predatory attack [186]; (3) infusion of an opioid agonist into the BNST results in suppression of defensive rage [51]. The nucleus accumbens modulates defensive rage elicited from the medial hypothalamus [52].

2.2. Neural substrates of aggressive behavior in the rat

2.2.1. Relationship of anatomical loci to hypothalamic attack responses and structure of the hypothalamic attack area

The first studies in rat, conducted with limited numbers of implanted electrodes, suggested that different types of aggression could be induced from different hypothalamic areas. In contrast to these reports [12, 105, 108, 161–163, 223, 231], it was later found that the whole region of the HAA basically yields the same set of aggressive responses, and that the variations in response can be accounted for by the intensity of stimulation, posture of the opponent, and the simultaneous activation of concomitant responses [114, 116, 118, 120–123]. If one compares the regions of the hypothalamus where other investigators [12, 105, 108, 161–163, 173, 223, 231] elicited aggressive responses

with the systematic distribution studies by Kruk and coworkers [114, 119, 120], taking into consideration the dimensions of electrodes and stimulation techniques used, it seems clear that all these responses have been induced in a subforaminal area (Fig. 6). It is likely that all these responses were obtained from the same neural system within that area.

HAA extends laterally from the arcuate nucleus and medial aspect of the ventromedial nucleus to the ventral aspect of the lateral hypothalamus. It extends rostrally from the lateral edge of the ventromedial nucleus towards the frontal pole of the ventromedial nucleus and anterior hypothalamic nucleus [113, 114, 119, 120]. HAA is approximately the same in male and female rats [114, 119] as well as in different strains of rats [115, 120]. Lesions of HAA reduce aggression evoked by an intruder in a territorial setting [8, 154, 159]. Marginal sites within HAA yield less intense responses. These studies suggest that a specific hypothalamic mechanism is involved in the control of aggression, although the sites producing aggression are not limited to a single nuclear group. See Figs. 6 and 7.

Following a novel classification of hypothalamic areas based on cytoarchitectonic criteria [81, 82], it is now recognized that HAA almost completely coincides with

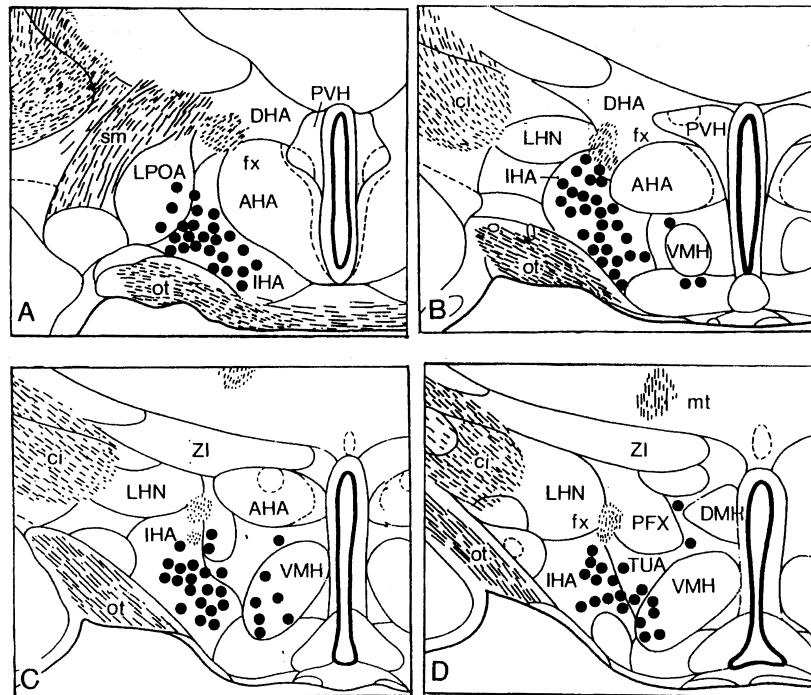


Fig. 6. Attack-inducing sites in the hypothalamus of the rat plotted in the atlas of Geeraedts et al. [81, 82]. Adapted from Ref. [175]. The attack area largely coincides with the intermediate hypothalamic area, and the ventro-lateral pole of the ventromedial nucleus of the hypothalamus. Abbreviations: AHA, anterior hypothalamic area; ci, capsula interna; DHA, dorsal hypothalamic area; DMH, dorsomedial hypothalamic nucleus; fx, fornix; LHN, lateral hypothalamic nucleus; LPOA, lateral preoptic area; mt, mammillothalamic tract; ot, optic tract; PFX, perifornical nucleus; PVH, paraventricular hypothalamic nucleus; sm, stria medullaris; VMH, ventromedial hypothalamic nucleus; ZI, zona incerta.

the intermediate hypothalamic area (IHA). IHA is about 0.5 mm^3 in size, and contains about 17×10^3 neurons and about 150×10^6 synaptic contacts. About half of these contacts are symmetrical contacts, the other half being asymmetrical. The synapse-to-neuron ratio is about 9×10^3 , whereas there are only 170 axo-somatic contacts per soma. IHA may be homologous to the anterior hypothalamus in the cat. The projection from the lateral septal area to the HAA consists of small unmyelinated varicose fibers forming axo-dendritic asymmetrical contacts in the IHA [1]. We assume that hypothalamic aggressive responses are elicited by the overriding of local tonic inhibition, since local infusion of the GABA_A antagonist bicuculline induces similar attacks [174]. Similar results were reported for the GABA antagonist picrotoxin [9], and for the combination of a glutamate agonist and bicuculline [91].

2.2.2. Efferent pathways involved in hypothalamic attack in the rat

In the rat, as in the cat, the hypothalamic attack area projects extensively to the PAG. In rat, in the regions of the PAG which receive projections from HAA, attack similar to hypothalamic attack can be elicited, although not as easily as from HAA [147], and the responses are sometimes accompanied by severe motor disturbances. However, selective destruction of the entire PAG only slightly and transiently reduces attack elicited by hypothalamic stimulation and aggression provoked by an intruder in a territorial

setting [148]. This differs from the cat, in which such lesions block aggression elicited by stimulation of the stria terminalis [72]. In the rat, though HAA efferents clearly differ from the efferents of the HGA, which is located in the paraventricular nucleus and adjacent dorsomedial hypothalamus, they may not be specific for attack behavior, since lesions of the PAG do not significantly affect hypothalamic attack or hypothalamic self-grooming [148, 220]. The effects of hypothalamic stimulation are possibly mediated by the ventro-caudal projections of HAA (see also [9]).

Stimulation of HAA activates ascending projections terminating in and projecting through the medial preoptic area [173, 175] where, occasionally, attack has been induced in the proximity of the ventral supraoptic commissure. This commissure, which may connect to neurons in the IHA/HAA or the adjacent anterior hypothalamus, has been suggested as a key element in the attack-relevant mechanisms in the hypothalamus [173]. Moreover, Adams [9] has shown that the GABA antagonist picrotoxin elicits aggressive behavior when injected into the area where electrical stimulation elicits attack, but also in the adjacent frontal area, ventrally in the anterior hypothalamus.

In the cat, clear-cut anatomical boundaries are present for different aggressive responses. In the rat, the apparent absence of such boundaries has complicated the task of tracing the connections of the system to more caudal regions of the brainstem, where a similar form of attack can be induced by electrical stimulation [147, 226]. However, the

projections of the IHA have now been studied in detail using the *Phaseolus vulgaris* leucoagglutinin (PHA-L; see Fig. 7) [175]. It now seems likely that HAA projects to many areas that affect aggression [226]: its projections pass through several of the structures relevant for aggression in the cat, such as the ventral tegmental area (VTA), raphe magnus, PAG, locus coeruleus, the A5 region of the brainstem tegmentum, and the nucleus tractus solitarius, and are covered with varicosities or *boutons-en-passant*, which may release neurotransmitter into these structures. These projections presumably subserve similar functions as suggested for the cat (i.e. autonomic or endocrine integration, or feedback loops). For a discussion of the involvement of endocrine mechanisms and hypothalamic behavioral regulation see Ref. [66].

2.2.3. Specificity of the projections from HAA/IHA

PHA-L tracing studies by Roeling and coworkers [175, 176] make it possible to get an impression of the behavioral specificity of HAA and HGA efferents. These studies revealed eight different streams of thin unmyelinated varicose efferents from each of these areas. The streams from HAA split and end in at least 26 different areas, projecting frontally as far as the nucleus accumbens and the lateral septum, dorsally as far as the lateral habenular nucleus and caudally as far as the nucleus of the solitary tract and ventrolateral medulla. The projections from HGA are similar. Fibers also emerge from HGA in eight unmyelinated streams, covered with varicosities, follow paths very similar to those from HAA, and terminate in at least 23 areas. At least 14 brain areas receive similar projections from both HGA and HAA (Table 1). These similarities suggest either

that the majority of the projections from these two areas have nothing to do with the specific behavioral consequences of stimulation, or that the behavioral specificity is due to subtle differences in projections within the target structures. There are indications for the latter explanation. Fig. 7 illustrates how HGA and HAA efferents have different preferences for specific structures. As expected, HGA, but not HAA, projects clearly to the arcuate nucleus and median eminence. Moreover, HGA projects much more extensively to the ventral tegmental area, raphe magnus, locus coeruleus and dorsal motor nucleus of the vagus and nucleus tractus solitarius. HGA projects to ventrolateral PAG, whereas HAA projects to dorsal and dorsolateral PAG. Since aggressive behavior is associated with high arousal, and grooming is associated with the absence of arousal, it is interesting to note that the parts of the PAG efferent to HAA are associated with blood pressure increases whereas parts efferent to HGA are associated with decreases. HAA projects preferentially to the adjacent ventromedial nucleus of the hypothalamus and to the parataenial and mediadorsal thalamic nuclei; HGA projects preferentially to the medial preoptic area and anteroventral parts of the periventricular nucleus. The most pronounced differences between HGA and HAA are found in the projections to the lateral septal nucleus: HGA projects almost exclusively to the ventral part of this nucleus, whereas the HAA projects almost exclusively to the dorsolateral portion of the intermediate part [175, 176]. The septal projections of the HAA are of interest because the lateral septum sends projections to the HAA, suggesting that the rage that is a well-known consequence of the interruption of septal–hypothalamic connections [10, 11, 13–16] may be

PREFERENTIAL EFFERENTS OF 'ATTACK' AND 'GROOMING' AREAS

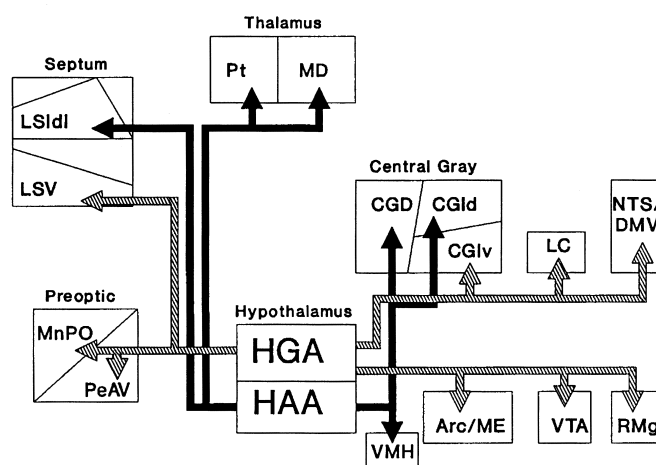


Fig. 7. Schematic representation of the specific projections of the hypothalamic attack area (HAA), as contrasted with the projections specific to the hypothalamic grooming area (HGA). For details on the 16 areas to which both HAA and HGA project (not shown here) see Refs. [175, 176]. Abbreviations: Arc, arcuate nucleus; CGD, dorsal part of the PAG; CGId, dorsal portion of the lateral part of the PAG; CGlv, ventral portion of the lateral part of the PAG; DMV, dorsal motor nucleus of the vagal nerve; LC, locus coeruleus; LSIdl, dorsolateral portion of the intermediate part of the lateral septal nucleus; LSV, ventral part of the lateral septal nucleus; MD, mediadorsal thalamic nucleus; ME, median eminence; MnPO, median preoptic nucleus; NTS, nucleus of the solitary tract; PeAV, anteroventral part of the periventricular nucleus; Pt, parataenial thalamic nucleus; RMg, raphe magnus; VMH, ventromedial hypothalamic nucleus; VTA, ventral tegmental area.

Table 1

Brain areas receiving projections from both the hypothalamic grooming area (HGA) and the hypothalamic aggression area (HAA), according to PHA-L injections (adapted from Refs. [175, 176]). Only areas that received projections in all rats injected at attack sites and all rats injected at grooming sites are listed

Amygdaloid area
Anterior commissure
Bed nucleus stria terminalis
Central tegmental field
PAG, pons
Lateral hypothalamic area
Lateral habenular nucleus
Lateral preoptic area
Lateral septal nucleus, intermediate part
Lateral septal nucleus, ventral part
Mesencephalic PAG
Medial amygdaloid nucleus
Medial preoptic area
Paraventricular thalamic nucleus
Substantia innominata, pars subcommissuralis
Substantia innominata, pars sublenticularis

due to interruption of a feedback loop [10, 11, 13, 14, 16, 43]. Moreover, HAA projections form peculiar pericellular baskets around septal cells that could interact with the serotonergic baskets around septal cells [80]. Thus one can speculate that the effects of serotonin agonists on hypothalamic attack [112, 113] and on aggression induced by other means [155, 157, 158] are due to interference with a HAA–septal feedback loop.

The fact that HAA projects to an area does not prove that such a projection mediates hypothalamic attack. Clues about the involvement of specific areas could be derived from the study of the patterns of activation caused by stimulation of IHA/HAA. However, an extensive study by Roberts and Nagel, utilizing deoxyglucose uptake as a metabolic marker during stimulation of sites in HAA [173], is hard to reconcile with the PHA-L projection studies. In this study, hypothalamic sites that produced upward flight behavior were used as controls for specificity of effects. Deoxyglucose uptake in 62 sites was quantified. Deoxyglucose labeling was more intense on the side of the brain ipsilateral to stimulation in both attacking rats and controls. Thirty-two brain areas were significantly more activated in attacking rats than in controls. Curiously, there were more differences from the controls at contralateral sites (28 differences) than ipsilateral sites (21 differences). In contrast, in the PHA-L studies, contralateral projections from the HAA/IHA were not much in evidence [175]. Based upon the deoxyglucose data and data from the general anatomical literature, but not from the PHA-L studies, a model was proposed by Roberts. According to this model, the efferents for aggression run from the HAA, via the ventromedial nucleus of the hypothalamus (VMH), to the ipsilateral and contralateral ventral supraoptic commissure to continue to the ventral zona incerta, the subparafascicular nucleus, the peripeduncular nucleus and the cuneiform area in the brain stem. Also

according to this model, four visual areas (the lateral superior colliculus, the lateral pretectal area, and the dorsal and ventral lateral geniculate nuclei) are preferentially activated during HAA stimulation, but the PAG is not.

Some support for this model is given by the facts that: (1) hypothalamic aggression has, on occasion, been elicited by stimulation of the region anterior and ventral to the HAA, proximal to the optic tract; (2) the HAA extends from the IHA into the ventrolateral part of the VMH [119, 123]. However, only the VMH, zona incerta and cuneiform area have been shown to be connected directly to the HAA, and only the ventrolateral part of VMH is considered as part of the aggression-relevant network in the study by Roeling and coworkers. Roberts' study suggests that the peripeduncular nucleus is most specifically associated with the HAA, and the septal area has no place in Roberts' proposed model [173]. Roeling and coworkers suggest that the most specific output pathway for the HAA is a specific part of the lateral septum, and the peripeduncular nucleus is absent from the projections studied by them. It should be noted that, in the cat, a pathway from the lateral hypothalamic-predatory attack region to the lateral septal area has been identified [75]; these authors interpreted this pathway as a feedback projection.

Four methodological reasons could explain the conflicting conclusions derived from these rat studies. First, the brain activity in anesthetized animals which are continuously stimulated for long durations, at suprathreshold intensities, may differ from the activity induced during the milder, short stimulations used to elicit attacks in awake animals. Second, even though the electrodes are in the same area as in other studies (i.e. in the IHA), larger areas may have been activated. Third, stimulation may also have had antidromic effects; therefore, deoxyglucose methods may reveal projections to and from the HAA, whereas PHA-L reveals only the latter. Fourth, the emphasis on the predominance of contralateral effects in the deoxyglucose study may be due to the statistical method used to demonstrate behavioral specificity by contrasting hypothalamic flight against hypothalamic attack. However, the raw data in that study clearly show that the ipsilateral effects are at least as prominent as the contralateral effects. The conclusion can only be that many pathways may be responsible for stimulation-induced aggression, and that additional studies and novel methods (e.g. c-Fos) are required to unravel the circuitry.

2.2.4. Functional relationships of other limbic structures to hypothalamic attack in the rat

The HAA overlaps with the projection areas of the medial amygdala to the medial hypothalamus [113, 114, 119, 120, 130]. Infusion of arginine-vasopressin (AVP) into the medial amygdala increases territorial aggression and partially counteracts the gradual decrease in territorial fighting caused by castration [109]. It is known that the expression of endogenous central vasopressin is dependent on

testosterone. Therefore, it is notable that castration causes increases in hypothalamic attack thresholds that can be reversed by testosterone [33]. Ovariectomy does not affect thresholds [114]. Infusion of the serotonergic drug, quipazine, into the medial amygdala reduces natural mouse killing [166]. In addition, the medial amygdala in the rat and cat seems to have a role in the learning of social signals and the significance of defeat [3, 109, 130, 224]. As noted above, connections of the amygdala with the hypothalamus may control hypothalamic attack release mechanisms with respect to these aspects of aggression.

Stimulation of the deeper orbital layers of the prefrontal cortex inhibits attacks elicited from the hypothalamus in rats [65]. This parallels the findings in the cat, where stimulation of the lateral or medial prefrontal cortex blocked predatory attack elicited from the lateral hypothalamus [203, 204]. The pathway mediating this effect may be a multisynaptic projection from the prefrontal cortex to the lateral hypothalamus, via the mediodorsal and midline nuclei of the thalamus [209].

3. The neuropharmacology of brain-stimulation-induced aggressive behavior

Studies of neurotransmitter involvement in stimulation-induced aggression have employed two approaches. In the first approach, an agonist and/or antagonist for the putative transmitter is injected systemically and the effect of the injection upon the threshold or latency is measured over time. This approach can provide an overall assessment of whether the transmitter is involved in aggression. In addition, it has the advantage of constituting the clinical route of administration of drugs such as carbamazepine. The deficiency of the approach is that it does not reveal the locus of action of the drug. In addition, with the use of this approach, one must determine whether the effects of drug administration are specific to the process under investigation. In the second approach, the agonist or antagonist is microinjected into a specific region within the brain, usually at an attack site, and the effects of drug infusion are identified. It should be noted that the use of cannula-electrodes allows investigators to electrically stimulate an area and to infuse a drug or retrograde tracer into the same area. This approach can provide clues about the presence or absence of a putative transmitter at a given synaptic region and its possible role in aggression, with four caveats. First, it is entirely possible that a receptor is present at a synapse, while the neurotransmitter usually associated with that receptor is not present. In such a case, the drug would act upon receptors at the synapse, resulting in a change of behavior, and this would lead one to the false conclusion that the transmitter at that synapse has been identified. Second, this approach can lead to a “fishing expedition” in which many different drugs are tested without a suitable rationale, unless there is a sound rationale that the transmitter is present at the synaptic

region. Third, with the microinjection technique, drug concentrations may exceed concentrations of the amine or peptide that normally acts at these receptor populations; for this reason, it is possible that systemic and intracerebral microinjections of a compound may yield different results. Fourth, if the volume of injection is too large, the drug may diffuse through the brain to affect areas other than the target area, as may have been the case for Ref. [99].

In the rat, much work has examined the involvement of neurotransmitters in aggression. However, since most of these studies have not used brain stimulation to elicit aggression, they fall outside the scope of this review. See the review by Miczek et al. [142] for an account of this research.

3.1. Evidence for the presence of a cholinergic mechanism in the cat

3.1.1. Systemic injections

Several early studies demonstrated that systemic injections of muscarinic agonists could facilitate defensive rage in the cat [83, 124, 234]. Berntson and Leibowitz [37] extended these findings by showing that injections of the muscarinic agonist, arecoline, could induce biting attack, which, in turn, was blocked by pretreatment with the muscarinic antagonists atropine or scopolamine. A later study [35] showed that pretreatment with nicotine can suppress naturally evoked or arecoline-induced predatory attack and defensive rage. Similar results were also observed by Katz and Thomas [100] who noted that the threshold for hypothalamically elicited predatory attack was elevated following scopolamine administration. However, Baxter [30] noted that atropine or scopolamine had little effect upon hypothalamically elicited defensive rage, other than to produce ataxia. Interestingly, scopolamine does not affect thresholds for hypothalamic attack in rats; perhaps the stimulation overrides or bypasses local cholinergic blockade [112, 118].

3.1.2. Intracerebral injections

Further support for the notion that muscarinic receptors are involved in the expression of aggression was gained from several studies. Beleslin and Samardzic [31] observed hissing and growling following intraventricular injections of muscarine chloride, which could be blocked by atropine or scopolamine. Such effects have also been reported when carbachol was placed into the medial hypothalamus [45, 46, 99, 177, 178, 221] or PAG [29, 94]. In an extensive mapping study, Allikmets [17] injected acetylcholine into defensive rage sites and observed similar behavioral effects; these sites were primarily localized to the periventricular hypothalamus and PAG. Defensive rage can also be observed following cholinergic stimulation of the septal area [94] or dorsomedial amygdala [18], areas usually considered to be modulatory. However, these areas have low thresholds for epileptiform activity, and stimulation of

them produces attack behavior only at current levels which produce seizures [200, 201]. Thus, the responses observed by these authors may have been secondary to seizure activity induced by chemical stimulation. Somewhat surprising results were obtained by Kono and coworkers [106, 107] who administered intrahypothalamic injections of acetylcholine or carbachol. They noted that low doses of these drugs did not alter spontaneous behaviors, but suppressed electrically elicited defensive rage. In contrast, higher doses elicited defensive rage. Further, choline or physostigmine elevated attack thresholds, whereas nicotine was ineffective; these inhibitory effects were antagonized by atropine but not curare, further supporting the notion that muscarinic mechanisms are involved. They also observed that the effects of microinjections of acetylcholine into the medial hypothalamus were blocked when lesions were placed into the stria terminalis, which led them to conclude that this pathway is cholinergic [107].

Regarding predatory attack, one study reported that carbachol microinjections into the ventral tegmentum of cats produced defensive rage followed by directed killing of a mouse [99]. The fact that both types of aggression followed the injections suggests that they activated a wide area containing separate regions for each form of attack.

These studies indicate that cholinergic drugs act through muscarinic receptors in the medial hypothalamus and PAG to modulate defensive rage and (possibly) predatory attack. However, a more convincing experiment to show that acetylcholine is involved in aggression would require that microinjection of a cholinergic antagonist into a synaptic region critical for the expression of attack inhibits that response when elicited either under natural conditions or by stimulation of another attack site.

3.2. Evidence for serotonergic involvement in attack behavior in the cat

3.2.1. Systemic injections

A serotonergic mechanism may be involved in aggression, as suggested by the consistent effects of systemically injected PCPA. For example, in one study PCPA induced both hypersexuality and predation [71]. Furthermore, several studies showed that PCPA facilitates (i.e. shortens the latency and lowers the threshold for) hypothalamically elicited predatory attack [100, 133]. One site where serotonin probably acts to modulate this response is the trigeminal motor nucleus, which is needed for biting to occur. Support for this view was provided by MacDonnell and Fessock [132] who demonstrated that evoked potentials in the trigeminal motor nucleus elicited by stimulation of parts of the basal ganglia from which jaw-opening could also be elicited were enhanced by PCPA treatment. These effects may not be limited to the cat: PCPA reduces natural predation time of the grasshopper mouse upon crickets [141]. Regarding defensive rage behavior, systemic administration of PCPA facilitates this response [133]; and in the rat, PCPA

is the only drug that facilitates hypothalamically elicited attack [118].

Other indirect evidence in support of a serotonin mechanism is that acute treatment with the tricyclic antidepressants chlorimipramine and imipramine (which may be more effective against catecholamines) suppresses predatory attack in the cat [68, 69]. These drugs are believed to inhibit preferentially the uptake of amines in serotonergic neurons when administered acutely [53]. In addition, if the animal is pretreated with PCPA, chlorimipramine does not suppress attack, suggesting that endogenous levels of serotonin are required for the antidepressant's inhibitory effects. Furthermore, when the animals were treated with the serotonin precursor 5-hydroxytryptophan (5-HT), the suppressive effects of chlorimipramine were restored. It is of interest to note that acute imipramine administration does not suppress defensive rage [68] and, in fact, even facilitates this response [137, 164]; this may be due to an elevation of norepinephrine levels (see discussion below). Chronic administration of tricyclics might have different effects on feline aggression. It is possible that since tricyclics, like the selective serotonin reuptake inhibitor paroxetine, elevate levels of 5-HT in the synaptic cleft when administered acutely, they, like paroxetine, also lead to a down-regulation of 5-HT₂ receptors when given chronically. Since acute treatment of rats with antidepressants results in a decrease in aggression, whereas chronic treatment results in an increase, an effect possibly due to down-regulation of 5-HT₂ receptors [146], perhaps chronic treatment of cats with tricyclic antidepressants would enhance predatory attack and/or defensive rage.

3.2.2. Intracerebral injections

In two separate studies, Golebiewski and Romaniuk [86] and Romaniuk et al. [179] demonstrated that serotonin, injected into hypothalamic sites from which carbachol can elicit affective defense, inhibits the attack response. Conversely, when methysergide, a serotonin antagonist, is injected into such sites, the attack response is enhanced. Moreover, when 5,6-dihydroxytryptamine (5,6-DHT), which selectively destroys serotonin neurons, is microinjected into the dorsal raphe, there is a decrease in brain serotonin coupled with an enhancement in carbachol-induced defensive rage. Thus, it is reasonable to conclude that serotonin normally serves to suppress defensive rage by acting, at least in part, upon neurons in the medial hypothalamus.

The raphe system projects to the forebrain, brainstem tegmentum, limbic system and even the trigeminal motor nucleus. A recent set of experiments tested the effects of microinjections of selective 5-HT compounds into the PAG upon defensive rage elicited from the medial hypothalamus [188]. Defensive rage was suppressed following microinjections of the 5-HT_{1A} receptor agonist, 8-OHDPAT; pretreatment of the PAG with microinjections of the 5-HT_{1A} antagonist p-MPPI blocked this effect. Facilitation of

defensive rage followed microinjections of the 5-HT_{2/1C} agonist, (+) DOI hydrochloride [188].

However, these studies did not fully identify (1) the sites where serotonin affects neurons associated with attack, (2) the actions of the respective 5-HT subtypes upon aggression, or (3) the cellular mechanisms of action of each of the subtypes.

3.2.3. Effects of serotonergic agents upon hypothalamic attack in the rat

In an initial set of experiments, PCPA was shown to decrease 5-HT levels and facilitate hypothalamic attack [118]. Similarly, infusion of 5,7-DHT, into the hypothalamus resulted in similar facilitation of “offensive” aggression in territorial fighting [222]. For a review of the involvement of serotonin and other transmitters in aggressive behavior, see Ref. [143].

In a series of studies, the effects of “serenic” compounds (which have high affinities for 5-HT receptors [158]) upon hypothalamic attack thresholds were determined using an up-and-down procedure (variation of the Method of Limits) [112, 114, 117, 118, 219, 230]. Drugs and doses were chosen which severely affect territorial or maternal aggression. Whenever possible, concomitant responses such as teeth chattering, locomotion and escape elicited from the same electrodes were used as controls for behavioral specificity. Details on procedures can be found in Refs. [118, 219]. Table 2 summarizes the effects of drugs on thresholds, obtained by different groups in different strains of rats. The effects are expressed as percentage increase with respect to vehicle control. All drugs were tested in adult males, except alcohol which was tested in adult females. All drugs have been shown to inhibit aggression in natural settings such as territorial or maternal aggression, and usually at lower doses than used here. Only a few drugs strongly increased thresholds. The phenyl-piperazines quipazine, “serenic” compounds fluprazine and its metabolite TFMPP, but also DL-propranolol, selectively elevated thresholds and also displayed steep parallel dose–effect curves, suggesting a common mechanism of action. Fluvoxamine and oxazepam weakly affected thresholds. In contrast, DL-amphetamine, scopolamine, 8-OH-DPAT (a selective 5-HT_{1A} agonist), mianserine (a 5-HT₂ antagonist) and chlordiazepoxide had no effect.

The inhibitory effects of propranolol could be due to its affinity for central 5-HT receptors [88, 144, 145] or to adrenergic blocking properties. The drug has a stereospecific effect on territorial aggression [233] and hypothalamic attack (Kruk, unpublished results). Fluprazine and propranolol facilitate social cooperation between rats in the same way [32]. Interestingly, propranolol and TFMPP have similar discriminative stimulus properties [85].

Strikingly, many drugs that affect aggression in natural settings do *not* affect hypothalamic attack. Thus, modulation

of hypothalamic attack in the rat by a limited class of serotonergic drugs, acting perhaps through 5-HT_{1B} receptors, seems to parallel the overall suppressive effects of this neurotransmitter upon aggressive reactions reported above in the cat.

The behavioral selectivity of the effects of serotonergic drugs was demonstrated by the fact that other behavioral consequences obtained from the same electrodes in the same animals were hardly affected by these drugs. Conversely, stimulation-induced locomotion was facilitated by scopolamine and amphetamine at doses that did not affect hypothalamic attack elicited from the same sites. The pharmacologic profile of stimulation-induced teeth chattering and escape resembles the profile of attack.

3.2.4. Comment

The overall results obtained in cat and rat indicate that serotonin mechanisms suppress aggression. Moreover, for the rat, the combined results of studies involving lesions, infusions of selective neurotoxins into the hypothalamus [8, 154, 160, 222], or application of selective anti-aggressive drugs acting through 5-HT receptors, strongly suggest that the hypothalamic attack release mechanism is involved in aggression in natural settings.

The following line of evidence supports this conclusion. Fluprazine and TFMPP are prototypes of the so-called “serenics” which have high affinities for 5-HT₁ receptors [158], and have been shown to inhibit hypothalamic attack selectively in both sexes and in different strains (CPB-WEzob rats, albino random bred CPB-WI Wistar rats and Tryon Maze Dull rats) [112, 114, 118, 157, 158, 219]. Serenics also reduce “natural” aggression provoked by the presence of an intruder endangering offspring or territory [155–158, 160]. Behavioral sequence analysis of the effects of an early prototype of the serenics [155] in a territorial setting reveals that serenics do indeed inhibit the most violent parts of the agonistic pattern such as fighting and biting. The rest of the agonistic pattern remains relatively unaffected by these drugs. Thus, drugs that inhibit hypothalamic attack also inhibit attack in natural settings. In contrast, many drugs that do not inhibit hypothalamic attack do inhibit aggressive behavior in a territorial setting [160]. However, drugs such as scopolamine and amphetamine seem to achieve such effects by reducing aggressive postures due to the induction of stereotypy and locomotion [118].

It has been suggested that the anti-aggressive properties of the serenics are due to anxiety-promoting properties [101, 102]. Since the potent anxiolytic oxazepam slightly *inhibits* hypothalamic attack, such a conclusion may not be justified. Anxiogenics, such as inverse benzodiazepine agonists, have just begun to be studied [see section 3.9 for further discussion].

Table 2

Pharmacological profile of hypothalamic attack for systemically administered drugs in rats. Drugs that suppress hypothalamic attack increase the threshold current required to induce attack. The increases are expressed as a percentage of the vehicle condition. Only the effects at the maximum dose are given. Adapted from Refs. [112, 118, 158, 219]. Notice that PCPA (parachlorophenylalanine) facilitates hypothalamic attack, and hypothalamic attacks are relatively insensitive to many drugs that do affect other forms of aggressive behavior, and that, apart from the dopaminergic antagonist haloperidol, drugs displaying serotonergic agonism are among the most effective drugs

Drug	Increase from control (%)	Dose range (mg/kg)	Source
DL-Amphetamine	no change	0.5–2.0 i.p.	[112, 118]
Scopolamine	no change	0.25–1.0 i.p.	[112, 118]
Chlordiazepoxide	no change	5–20 p.o.	[112, 118]
Chlordiazepoxide	50 (at highest dose only)	5–20 p.o.	[158]
Oxazepam	8	5–20 p.o.	[112, 118]
Alcohol	no change	250–2000 p.o.	[118]
DL-Propranolol	35	5–20 i.p.	[112, 118]
Haloperidol	400–500	0.5–2.0 p.o.	[112, 118]
Naloxone	no change	1.25–10 i.p.	[118]
Phenytoin	no change	100 single dose p.o.	[118]
Carbamazepine	no change	50 single dose i.p.	[118]
8-OH-DPAT	no change	0.05–0.2 s.c.	[112, 118]
8-OH-DPAT	no change	0.125–1.0 p.o.	[158]
Mianserine	no change	3–30 i.p.	[112, 118]
Fluvoxamine	20	5–20 i.p.	[118]
Fluvoxamine	50	10–40 p.o.	[158]
TFMPP	83	0.5–2 i.p.	[112, 118]
Fluprazine	71	4–8 i.p.	[112, 118, 219]
Fluprazine	90	5–20 p.o.	[158]
Eltoprazine	140	2–8 p.o.	[158]
Quipazine	48	1.25–10 i.p.	[112, 118]
PCPA	– 9 (after 72 h)	375 single dose i.p.	[118]

3.3. Dopaminergic involvement in stimulation-induced attack behavior in the cat

3.3.1. Systemic effects

Dopaminergic mechanisms are thought to facilitate defensive rage and predatory attack. One indirect piece of evidence is that electrical stimulation of the ventral tegmentum or substantia nigra, the primary sources of dopaminergic innervation of the forebrain, facilitated defensive rage [63, 185]. Direct evidence was obtained by Maeda et al. [136] and Maeda and Maki [135] who showed that thresholds for hypothalamically elicited defensive rage decreased following systemic administration of the indirect and direct dopamine agonists methamphetamine and apomorphine respectively. Maeda and coworkers also showed that haloperidol, a non-selective dopamine antagonist, elevated the defensive rage threshold.

Another study replicated and extended these findings. First, it was found that haloperidol injected alone elevated thresholds, or, when injected before apomorphine, blocked its facilitatory effects. Then, these authors found that the relatively selective D₂ agonist, LY 171555 (Quinpirol), but not the selective D₁ agonist, SKF 38393, facilitated defensive rage. Moreover, the facilitatory effects of apomorphine or LY 171555 could be selectively blocked with pretreatment with either haloperidol or the specific D₂ antagonist, spiperone, but not with the relatively selective

D₁ antagonist, SCH 23390. Thus, it was concluded that dopaminergic facilitation of defensive rage is mediated primarily by D₂ receptors [212].

Predatory attack is also facilitated via D₂ receptors [190]. Apomorphine administration facilitated the occurrence of this response; and spiperone, but not SCH 23390 (a D₁ antagonist), elevated response thresholds when administered alone, and blocked the facilitatory effects of apomorphine when delivered before apomorphine. In conclusion, it would appear that dopaminergic mechanisms facilitate defensive rage and predatory attack, whereas serotonin inhibits these responses.

3.3.2. Intracerebral injections

Dopaminergic fibers from the ventral tegmentum and adjoining regions of the far medial hypothalamus project rostrally to the limbic forebrain and supply, among other regions, the medial anterior hypothalamus–preoptic zone, a region critical for the expression of defensive rage in both cat and rat. Accordingly, the model shown in Fig. 8 proposes that catecholaminergic fibers facilitate defensive rage, particularly at the level of the anterior medial hypothalamus (although interactions at other levels along the limbic-midbrain axis may also exist).

This hypothesis was directly tested in one study [213]. Stimulating electrodes were implanted into the region of the ventromedial hypothalamus and cannula-electrodes were

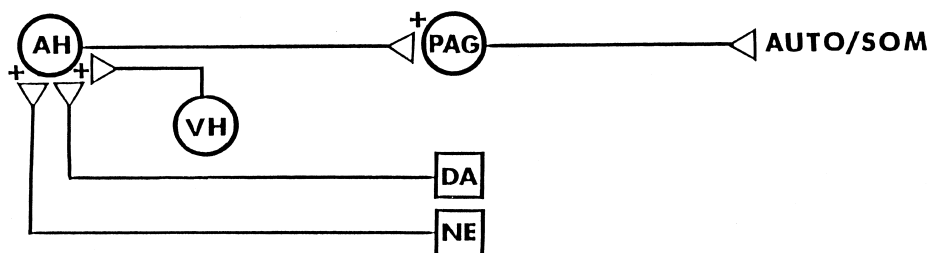


Fig. 8. Schematic diagram indicates the proposed circuitry involved in catecholaminergic facilitation of defensive rage behavior (elicited from the ventromedial hypothalamus). Note that an important site of interaction where catecholaminergic fibers produced facilitation of this response is the anterior hypothalamus. Abbreviations: AH, anterior hypothalamus; AUTO, autonomic cell groups of lower brainstem; DA, dopaminergic fibers; NE, noradrenergic fibers; PAG, midbrain periaqueductal gray; SOM, somatic cell groups of lower brainstem; VM, ventromedial nucleus.

implanted into the medial anterior hypothalamus–preoptic zone. Dopaminergic compounds were microinjected into defensive rage sites within the medial anterior hypothalamus–preoptic zone. In brief, microinjections of apomorphine or a relatively selective D_2 agonist, LY 171555 (but not a D_1 agonist, SKF 38393) facilitated defensive rage (see Fig. 9). Moreover, microinjections of either the non-selective antagonist, haloperidol, or the D_2 antagonist, sulpiride, but not the D_1 antagonist, SCH 23390, elevated response thresholds when injected alone into the anterior medial hypothalamus, and blocked the effects of apomorphine or LY 171555 when administered as a pretreatment. This result demonstrates that dopaminergic stimulation of the medial anterior hypothalamus–preoptic zone facilitates defensive rage behavior via D_2 receptors.

3.4. Noradrenergic involvement in stimulation-induced attack behavior

Early experiments suggested that norepinephrine facilitates attack. However, the data were not entirely consistent. One line of investigation [169–171] demonstrated that a selective decrease in brain norepinephrine follows defensive rage reactions produced by hypothalamic stimulation in the cat. These authors further showed that pre-collicular lesions produced recurrent defensive rage responses which were accompanied by decreases in norepinephrine content in the brainstem (in contrast to mid-collicular lesions, which were not associated with either defensive rage responses or changes in brainstem norepinephrine). The authors concluded that a fall in norepinephrine content is specific for defensive rage and further suggested that the central release of norepinephrine triggers the attack response.

3.4.1. Systemic injections

Several investigators examined the effects of D-amphetamine, which causes release and prevents the reuptake of catecholamines, upon predatory attack and defensive rage in the cat. Amphetamine administration was reported to facilitate defensive rage in one study [19], but in another it had no effect upon this response when elicited from the medial hypothalamus [30]. In rats, systemic DL-amphetamine, at doses that affect locomotion and stimulation-

induced escape, had no effect on hypothalamic aggression [112].

In an early study [198], systemic administration of amphetamine enhanced the facilitatory effects of reticular formation stimulation upon predatory attack elicited from the hypothalamus. Marini et al. [138] later demonstrated that low doses of DL-amphetamine facilitated predatory attack and higher doses inhibited it. When catecholamine levels in the brain were depleted following α -methylparatyrosine administration, a cat's approach toward a rat was blocked but reflexive biting remained intact [100]. In contrast, after catecholamine levels were antagonized by the dopamine β -hydroxylase (noradrenergic synthesis) blocker, disulfiram, hypothalamically elicited predatory

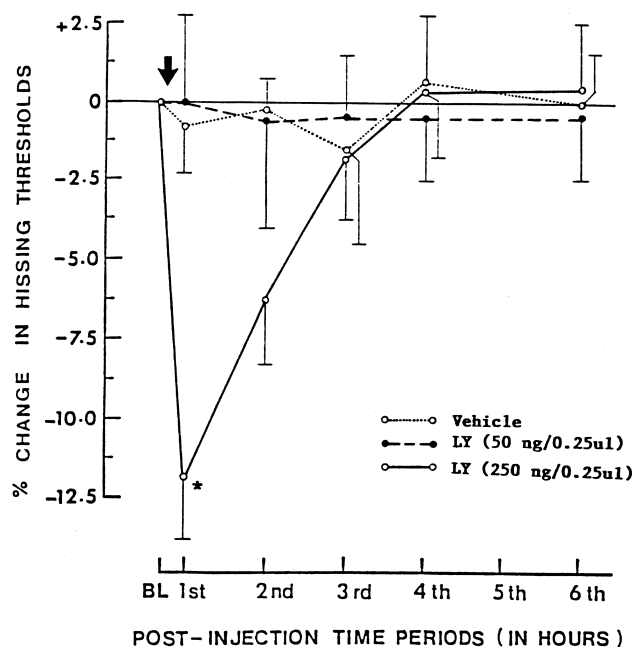


Fig. 9. Time course of the effects of microinjection of LY 171555 (50 and 250 ng/0.25 μ l) or vehicle (0.1% ascorbic acid) into the medial preoptico-anterior hypothalamic area upon ventromedial-hypothalamically elicited hissing. Each point represents the average change in hissing threshold current expressed as a percentage relative to preinjection baseline threshold. Arrow indicates time of injection. * $p < 0.05$ compared with vehicle. Bars = S.E.M.; $n = 5$ for each treatment. (From Ref. [213] with permission.)

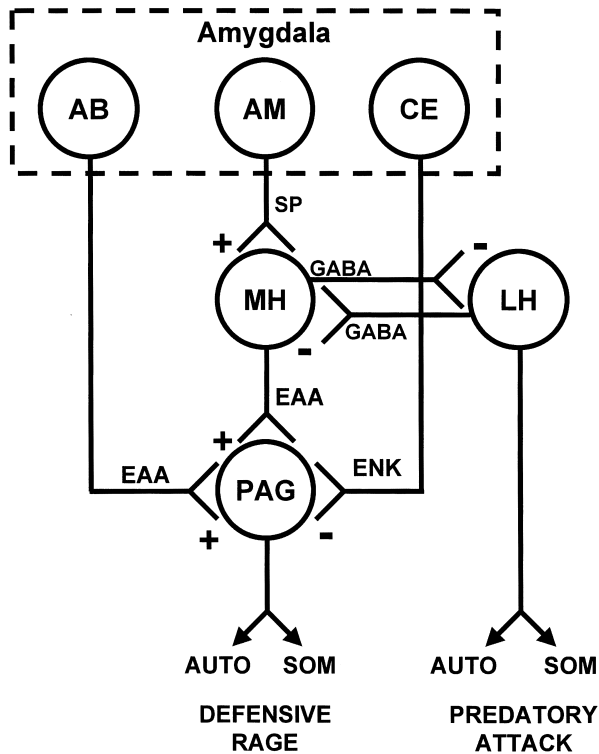


Fig. 10. Proposed model of functional relationship between amygdala, hypothalamus, and PAG with respect to the control of defensive rage behavior and predatory attack behavior. Note that processes excite defensive rage behavior by driving neurons in either the medial hypothalamus (MH) or midbrain periaqueductal gray (PAG). Because of the presence of an inhibitory GABAergic neuron that projects from the medial to lateral hypothalamus (LH), excitation of the mechanism for defensive rage will inhibit the mechanism for predatory attack. Cholecystokinin, norepinephrine, dopamine, and serotonin inputs are not shown but are important modulators of defensive rage and predatory attack. Other abbreviations: AB, basal amygdaloid complex; AM, medial amygdaloid nucleus; CE, central amygdaloid nucleus; AUTO, autonomic cell groups of lower brainstem; SOM, somatic cell groups of lower brainstem; EAA, excitatory amino acids; ENK, enkephalin; SP, substance P; +, excitatory pathway; -, inhibitory pathway.

attack was strongly inhibited [132]. While these studies suggest that predatory attack in the cat is facilitated by noradrenergic mechanisms, one study conducted in the rat reported inhibition of hypothalamic attack after systemic injection of the β -blocker, propranolol [112].

3.4.2. Intracerebral injections

Torda [214] induced defensive-like aggression in rats with the aid of foot shock and then observed that infusion of a cocktail of norepinephrine and dopamine into the medial hypothalamus facilitated this response. On the other hand, contrasting findings were observed in another study [84], where it was found that intraventricular infusions of dopamine increased shock-induced fighting, but norepinephrine reduced fighting. With respect to the cat, Mark et al. [139] induced defensive rage by placing lesions in the ventromedial hypothalamus. They observed that norepinephrine injections into the basolateral amygdala

suppressed this response as the animals appeared lethargic and placid. In another study, Romaniuk and Golebiewski [180] microinjected norepinephrine into sites within the medial hypothalamus of the cat where carbachol could elicit defensive rage and failed to observe any changes in behavior.

In more recent experiments [26, 27], whose rationale was virtually identical to that described above for Ref. [213], the underlying hypothesis was that noradrenergic fibers modulate neurons within the anterior medial hypothalamus. Accordingly, infusion of noradrenergic compounds into the hypothalamus should affect hypothalamically elicited defensive rage. In brief, infusion of either norepinephrine or the α -2 agonist, clonidine, into defensive rage sites within the anterior medial hypothalamus, facilitated that response when it was elicited from the ventromedial hypothalamus. Moreover, pretreatment with the α -2 antagonist, yohimbine, blocked the effects of both norepinephrine and clonidine. In contrast, phenylephrine (a selective α -1 agonist), propranolol (a β -blocking agent), terbutaline (a β -2 agonist), metoprolol (a β -1 antagonist) and butoxamine (a β -2 antagonist) had little or no effect on attack when microinjected alone or when used as a pretreatment for norepinephrine. Therefore, it is reasonable to conclude that the facilitating effects of norepinephrine upon defensive rage are mediated, in part, by actions on α -2 receptors in the anterior medial hypothalamus. See Fig. 8.

3.5. The role of neuropeptides in the regulation of feline aggressive behavior

3.5.1. Opioid peptides

Opioid involvement in aggression is suggested by the following evidence. First, it has been suggested, at the clinical level, that morphine reduces heightened levels of aggressiveness [103, 104, 232]. Second, in the cat, opioid receptors and enkephalin-containing cells and axon terminals are present in dense quantities in the PAG, central nucleus of the amygdala, BNST, and nucleus accumbens [20, 87, 89, 150, 167, 191, 192, 206].

3.5.1.1. Systemic studies in the cat. Three findings suggest that opioids selectively suppress defensive rage. First, systemic administration of naloxone lowered the threshold for defensive rage elicited from hypothalamus or PAG, in a dose-dependent manner [50, 195]. Second, predatory attack thresholds from hypothalamic sites were elevated by naloxone administration [50], whereas thresholds for PAG-elicited contralateral circling were unaffected. Third, fighting behavior induced in cats by intraventricular injections of carbachol was suppressed by subsequent intraventricular injections of morphine, suggesting that μ receptors may be important [111].

3.5.1.2. Intracerebral injections in the cat. The BNST and possibly the nucleus accumbens may receive opioidergic inputs from the central nucleus of amygdala [216], and

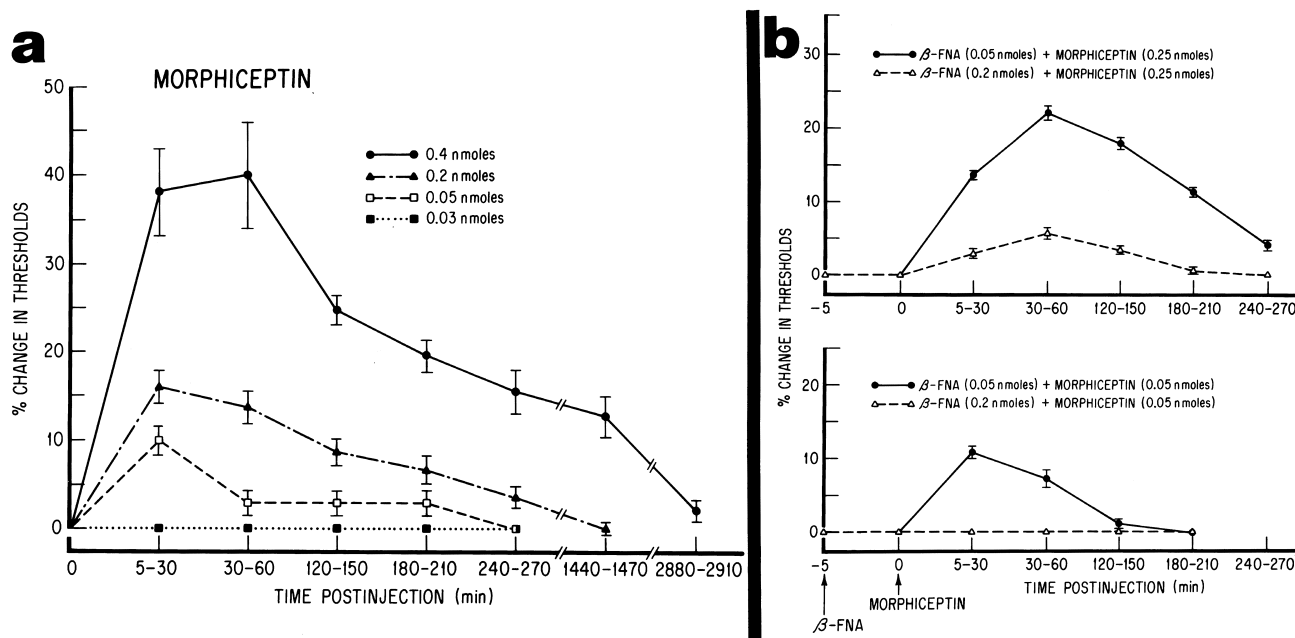


Fig. 11. (a) Morphiceptin, in doses of 0.05–0.4 nmol, suppressed PAG-elicited defensive rage in a dose- and time-dependent manner; (b) pretreatment with 0.2 nmol of β -FNA 5 min prior to morphiceptin administration into the same sites blocked the suppressive effects of morphiceptin (0.05 nmol). However, pretreatment with β -FNA at a dose level of 0.05 nmol did not block the suppressive effects of either dose of morphiceptin. Bars = S.E.M. (From Ref. [191] with permission.)

enkephalinergic cell bodies and axon terminals are present in the PAG [150].

Therefore, in separate experiments, the nonspecific enkephalin agonist D-Ala²-Met⁵-enkephalinamide (DAME) was microinjected into sites within the BNST and nucleus accumbens which modulated hypothalamically elicited defensive rage [51, 52]. At both of these nuclei, DAME elevated thresholds for modulation. Moreover, pretreatment of these sites with naloxone blocked the effects of DAME. This suggests that hypothalamically elicited (or PAG-elicited) defensive rage may be governed by an opioidergic input from the central nucleus, which, when activated, suppresses defensive rage. In fact, amygdaloid inputs can modulate the activity of neurons in the BNST via an opioid mechanism [64].

Two studies demonstrated that defensive rage [165] and predatory attack [229] are modulated within the PAG by an opioidergic mechanism. In one study [165], defensive rage was elicited from the medial hypothalamus and cannula-electrodes were placed into PAG sites which inhibited or facilitated this response. The results indicated that infusion of naloxone into inhibitory, but not facilitatory, PAG sites blocked the modulatory effects on hypothalamically elicited defensive rage. Furthermore, DAME infusion into inhibitory PAG sites inhibited hypothalamically elicited defensive rage. These results suggest that stimulation of inhibitory sites in the PAG activated enkephalinergic neurons arising from either the central nucleus of the amygdala or from within the PAG itself. Accordingly, infusion of naloxone

at these sites would prevent the enkephalins from suppressing the attack mechanism (see schematic diagram in Fig. 10).

There also exist PAG sites which facilitate and suppress predatory attack behavior elicited from the lateral hypothalamus. These modulatory sites are influenced by naloxone, suggesting that the enkephalinergic mechanism regulates predatory attack at the level of the PAG [229].

At least two questions were left unanswered by these studies. The first concerns the relevant subtypes of enkephalinergic receptors, and the second relates to whether enkephalinergic neurons situated outside the PAG project directly to defensive rage sites within the PAG. These two questions were addressed in three experiments. In the first experiment [194], DAME was infused into PAG defensive rage sites and it was observed that thresholds increased. Pretreatment with naloxone blocked the suppressive effects of DAME, and DAME did not affect PAG-elicited circling behavior. The conclusion was that enkephalinergic receptors in the PAG mediate suppression of defensive rage. In the second experiment, Shaikh et al. [191] sought to identify the receptor subtypes involved in the suppression of defensive rage at the level of the PAG. Infusion of morphiceptin, a μ agonist, into the PAG, increased thresholds for PAG-elicited attack with as low a dose as 0.4 nmol. A smaller increase was observed following infusion of DPDPE, a δ receptor agonist, but the κ agonist U-50488H, had no effect. Furthermore, pretreatment with μ and δ antagonists, β -Funtaltrexamine (β -FNA) and ICI 174864 respectively,

blocked the suppressive effects of morphiceptin and DPDPE respectively, indicating the importance of these receptor subtypes (see Fig. 11).

The third experiment is as follows. It is possible that opioidergic fibers constitute interneurons within the PAG that inhibit defensive rage when activated from an external source. Alternatively, opioid peptides may be synthesized in cell bodies located in the amygdala that project to the PAG, and, when activated, these neurons suppress defensive rage. In order to test this possibility, an experiment was performed. Initially, stimulation of the central or lateral nucleus produced a suppression of PAG-elicited defensive rage which lasted up to 30 min. When non-selective (naloxone) and selective μ (β -FNA) opioid antagonists were microinjected into PAG defensive rage sites prior to brain stimulation, the suppressive effects of amygdaloid stimulation were completely blocked (Fig. 12). However, a δ antagonist (ICI 174864) had no effect. Moreover, medial amygdaloid facilitation of PAG-elicited defensive rage was unaffected by infusion of naloxone into the PAG [192]. These results suggested that the central or lateral nucleus of the amygdala suppresses defensive rage at the level of the PAG and that the probable neurotransmitter is an opioid acting upon μ receptors. In order to test whether the opioid neurons were local interneurons or projection neurons from another structure, the retrograde tracer Fluoro-Gold was injected into PAG defensive rage sites. Cells double-labeled for Fluoro-Gold and met-enkephalin immunoreactivity were found in the central nucleus and immediately adjoining regions of the lateral and basal complex. Notably, cells situated within adjoining parts of the basal complex of amygdala, which facilitate defensive rage behavior (see fig. 21 of Ref. [201], are also double-labeled for Fluoro-Gold and aspartate or glutamate. Pending further pharmacological verification, this would suggest that this region of the basal complex directly facilitates defensive rage behavior at the level of the PAG, utilizing excitatory amino acids as a neurotransmitter.

3.5.1.3. Opioids in the rat. As noted previously, the nonspecific opioid antagonist naloxone does not affect stimulation-induced attacks in the rat [112].

3.5.2. Cholecystinin (CCK)

The neuropeptide CCK plays a role in anxiety responses. Since anxiety resembles defensive rage, in that both behaviors involve sympathetic arousal in response to a threatening stimulus, one study tested the effect of CCK on defensive rage in the cat [131]. Micro-injections of the CCK_B agonist pentagastrin into the PAG were found to facilitate defensive rage, whereas micro-injections of the CCK_B antagonist, LY288513, but not the CCK_A antagonist, PD140548, suppressed it. The specificity of this effect was demonstrated by the observation

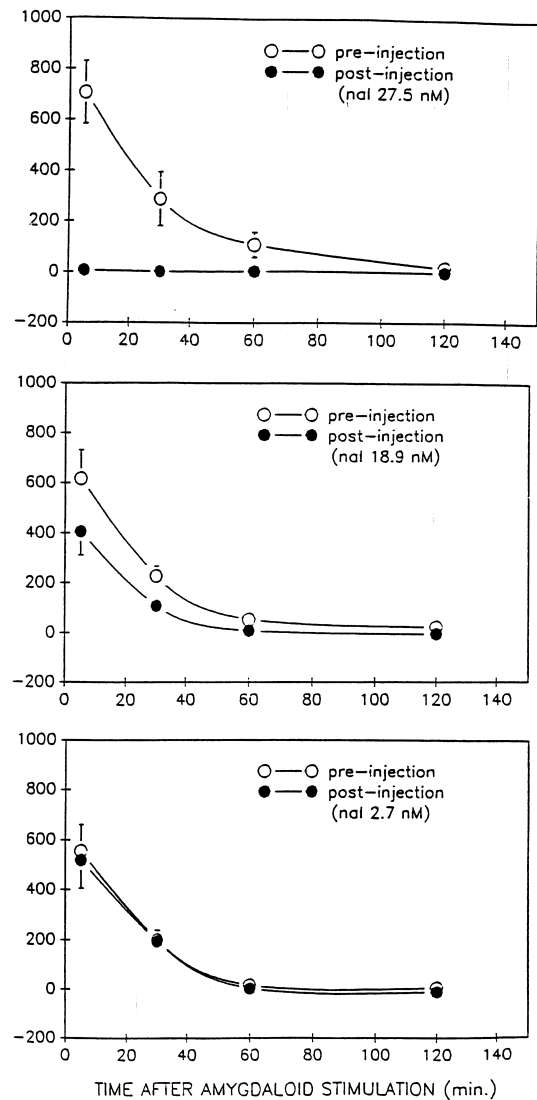


Fig. 12. Naloxone infusion into the PAG completely blocks the suppressive effects of central amygdaloid stimulation upon PAG-elicited defensive rage behavior in a dose-dependent manner. Open circles represent the time course for amygdaloid-induced suppression of defensive rage behavior as determined by the percentage change in response latencies from baseline values obtained prior to amygdaloid stimulation. These response latencies were obtained with single stimulation of the PAG following central amygdaloid stimulation. The latency values returned to baseline levels approximately 60 min after the last trial of amygdaloid stimulation. Closed circles indicate the effects of naloxone delivery. Mean data points for each of four epochs of time (5–30, 30–60, 60–90, and 120–150 min) are represented at the beginning of each period (with permission).

that infusion of the CCK_B antagonist into the PAG facilitated predatory attack.

3.6. Amino acid neurotransmitters

3.6.1. Pathways utilizing excitatory amino acids in association with the expression or modulation of aggression

Several studies suggest that excitatory amino acids are

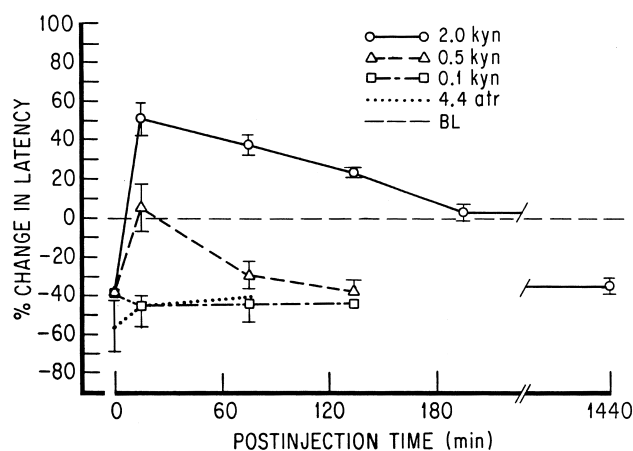


Fig. 13. Graphs indicate that infusion of kynurenic acid (kyn) into PAG sites, from which defensive rage behavior can be elicited, blocks the facilitatory effects of medial hypothalamic stimulation upon this response elicited from the PAG. This effect is dose- and time-dependent. Note that a relatively higher dose of atropine (atr) had little effect upon medial-hypothalamic stimulation-induced aggression. Abbreviation: BL, theoretical baseline values indicating the position on the graph where dual stimulation of the medial hypothalamus has no effect in altering PAG response latencies as determined from single stimulation of the PAG. All drug doses are in nanomole values. Vertical bars indicate S.E.M. for this figure (with permission).

released at the terminal endings of the fibers arising from the medial hypothalamus and projecting to PAG [129, 182, 183]. In one experiment, it was demonstrated that the nonspecific excitatory amino acid antagonist, kynurenic acid, microinjected into PAG attack sites, blocked the medial hypothalamic facilitation of PAG-elicited defensive rage, thus supporting the view that excitatory amino acids act at this synapse (Fig. 13). In additional experiments, infusion of the specific NMDA antagonist, AP-7, into the PAG, blocked medial hypothalamic facilitation, whereas administration of 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX), which selectively blocks kainate and quisqualate receptors, was ineffective. Moreover, infusion of NMDA into the PAG facilitated defensive rage elicited from the PAG, suggesting that NMDA receptors mediate the effect. Parallel findings were observed in a different experiment [182, 183]: hypothalamically elicited defensive rage was blocked following microinfusion of AP-7 into the PAG. Finally, another study combined retrograde labeling (following injections of Fluoro-Gold into the PAG) and immunocytochemical methods. Double-labeled cells for both Fluoro-Gold and aspartate or glutamate were found within the medial hypothalamus, dorsal and somewhat rostral to the level of the ventromedial nucleus, thus demonstrating that glutamatergic neurons project from hypothalamus to PAG. These data further serve to support the notion that an excitatory amino acid pathway governs the input to the PAG from the medial hypothalamus for the expression of defensive rage.

In a separate study, a dual-stimulation paradigm was

employed to test the hypothesis that the facilitatory effect of the basal complex of amygdala upon defensive rage is mediated over a pathway that projects directly to the PAG and whose functions are mediated by NMDA receptors [193]. The results showed that the facilitatory effects of basal amygdaloid stimulation could be reduced by microinjections of AP-7 into the PAG. That this NMDA antagonist did not block the attack response produced by single stimulation of the PAG indicates that the observed effects could not be attributed to anesthetic properties of the drug. Moreover, this study identified basal amygdaloid neurons labeled for both glutamate and Fluoro-Gold following microinjections of the retrograde tracer into attack sites in the PAG. Collectively, these findings support the view that basal amygdaloid facilitation of defensive rage is mediated in part by NMDA receptors over an excitatory amino acid pathway that projects from the basal amygdala to the PAG.

3.6.2. Excitatory amino acids and the elicitation of aggressive responses

Local infusion of excitatory amino acids has been utilized by many investigators to demonstrate that the effects of stimulation upon such events as single unit activity or autonomic processes were the result of activation of cell bodies rather than fibers of passage. In recent years, this approach has been extended to the study of aggressive and related emotional processes with mixed success. The most effective region where microinjections of glutamate, aspartate or D,L-homocysteic acid can elicit defensive rage behavior is the PAG in the cat [22, 184]. However, defensive rage sites in the medial hypothalamus are not responsive to microinjections of excitatory amino acids. In contrast, both electrical and chemical stimulation of the perifornical hypothalamus result in the elicitation of predatory attack [22]. In the squirrel monkey, electrical and chemical stimulation can elicit vocalization at a number of forebrain and brainstem sites, including the lateral hypothalamus, PAG, and lateral tegmental fields of the brainstem [98]. It should be noted that the failure to obtain a behavioral response by microinjection of an excitatory amino acid into a site where electrical stimulation has elicited the response does not necessarily mean that the response obtained by electrical stimulation was the result of stimulation of fibers of passage. Such a failure may be due to factors such as the diffuse arrangement of cells in the region or the insensitivity of these cells to excitatory amino acids.

3.6.3. Excitatory amino acids in the rat See Section 3.8.3.

3.7. The role of substance P in defensive rage and predatory attack in the cat

Stimulation of the medial amygdala facilitates defensive rage elicited from the medial hypothalamus, but suppresses predatory attack elicited from the lateral hypothalamus [201]. Moreover, the relevant projections from the medial

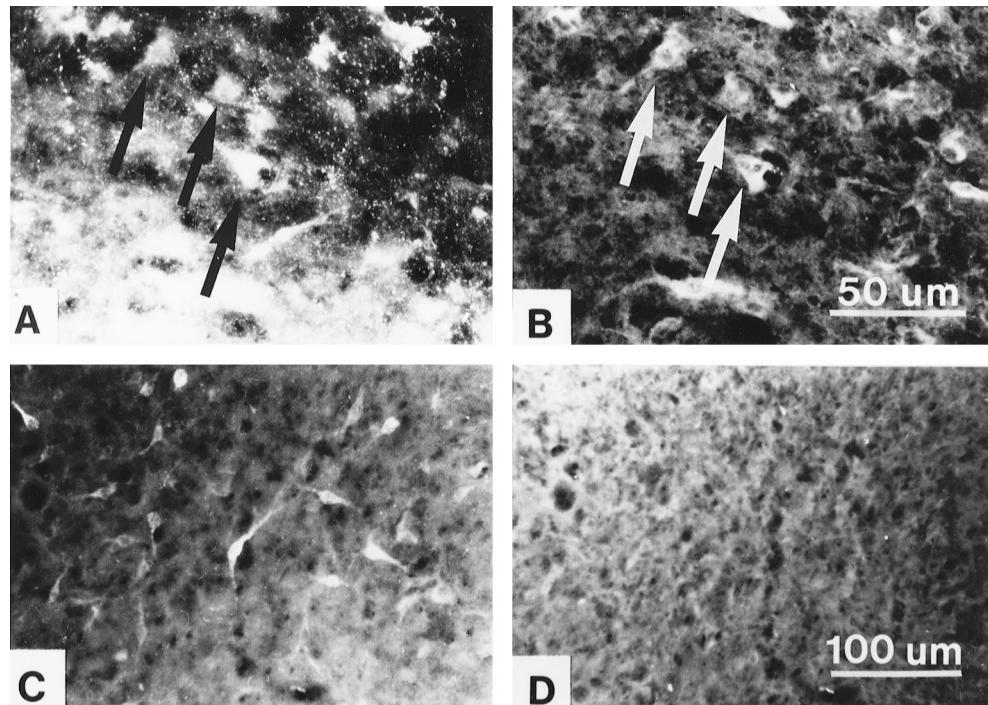


Fig. 14. (A,C) Microinjections of the retrograde tracer Fluoro-Gold into lateral hypothalamic sites, from which predatory attack behavior could be produced, resulted in labeled cells within the medial hypothalamus, demonstrating that medial hypothalamic neurons project to the lateral hypothalamus. (B,D) Immunocytochemical staining for GABA in the same brains showed that GABA-immunopositive neurons are present in the medial hypothalamus. Arrows in A and B indicate the presence of double-labeled cells, demonstrating that GABAergic neurons project from the medial to lateral hypothalamus. C and D indicate that some neurons in the medial hypothalamus stain positively only for Fluoro-Gold and not for GABA, suggesting that not all neurons which project from medial to lateral hypothalamus are GABAergic. (From Ref. [93], with permission.)

amygdala are directed through a monosynaptic pathway (i.e. the stria terminalis) to the medial hypothalamus [48, 211]. This implies that, while the effects of medial amygdaloid stimulation upon defensive rage, which is integrated within the medial hypothalamus, are *direct*, the effects upon predatory attack, which is integrated within the lateral hypothalamus, are *indirect*. The data presented below provide a likely mechanism that accounts for these effects.

3.7.1. Defensive rage

Medial amygdaloid stimulation facilitates defensive rage [48, 70, 211]. In one study, after this finding was replicated, the SP-neurokinin 1 antagonist, CP 96,345, was microinjected into the medial hypothalamus and this was found to block the facilitating effects of medial amygdaloid stimulation [197]. Moreover, following Fluoro-Gold microinjections into the medial hypothalamus, neurons labeled for both SP and Fluoro-Gold were found densely distributed within the medial amygdala but not elsewhere in the temporal lobe. These observations provided evidence that the effects of the medial amygdala upon defensive rage are mediated via a monosynaptic pathway that acts upon SP receptors in the medial hypothalamus.

3.7.2. Predatory attack

A sequel to this study, using similar methods, demonstrated that medial amygdaloid suppression of lateral

hypothalamically elicited predatory attack is also mediated, in part, through SP receptors in the medial hypothalamus [92]. Specifically, microinjections of CP 96,345 into the medial hypothalamus blocked medial amygdaloid suppression. However, since the SP pathway mediating suppression of predatory attack terminates in the medial hypothalamus, such modulation must require at least one additional neuron for these effects to take place. The only way to account for the inhibitory action of the medial amygdala upon predatory attack when the initial output neuron from that region is excitatory (i.e. an SP neuron) is to postulate the existence of a second, inhibitory neuron that projects from the medial to the lateral hypothalamus. It was further suggested that such a neuron is likely to utilize GABA as a neurotransmitter. An experiment undertaken to test this hypothesis is described below [93].

3.8. Inhibitory amino acids: GABA and glycine

3.8.1. Defensive rage

GABA serves as an inhibitory neurotransmitter at many CNS synapses. In an early study [152], GABA was injected into medial hypothalamic defensive rage sites. The results, surprisingly, showed that thresholds were actually lowered following drug infusion. In contrast, infusion of glycine into the same sites resulted in an elevation in thresholds, indicating a possible inhibitory role for this putative transmitter.

In a later study [196] cannula-electrodes were implanted into defensive rage sites within the dorsal PAG. Microinjections of the GABA agonist muscimol into defensive rage sites within the dorsal PAG produced elevations in threshold at as low a dose as 12 pmol. Muscimol had no effect upon predatory attack responses elicited from ventral PAG. In addition, pretreatment with bicuculline, a GABA_A antagonist, completely blocked the suppressive effects of muscimol [196]. Thus, it appears that GABA selectively modulates defensive rage by serving as an inhibitory transmitter within the PAG. Nevertheless, a number of questions remain unanswered with respect to the overall role of GABA in the PAG. For example, we do not know the specific receptor subtype(s) involved; nor do we know the origins of these GABA neurons. Are they local interneurons within a single functional column of the PAG [23]? Or do they originate from adjacent columns, or from distant regions of the forebrain and brainstem, and specifically project to sites within the PAG that mediate defensive rage behavior? Answers to these questions would help us understand how GABA affects defensive rage and related forms of emotional behavior.

3.8.2. Predatory attack and defensive rage: a reciprocal inhibitory pathway between the medial hypothalamus and lateral hypothalamus of the cat

As indicated above, it was hypothesized that medial amygdaloid suppression of lateral-hypothalamically elicited predatory attack was mediated through a GABAergic neuron that projects from the medial to lateral hypothalamus. To test this hypothesis [93], suppression of lateral-hypothalamically elicited predatory attack was induced either by electrical stimulation of the medial amygdala or by microinjection of SP into the medial hypothalamus. Suppression of predatory attack induced by either of these procedures could be blocked following microinjections of the selective GABA_A antagonist, bicuculline, into the lateral hypothalamus. Moreover, this study also demonstrated the presence of GABA receptors within the lateral hypothalamus as well as neurons in the medial hypothalamus that were labeled for both Fluoro-Gold and GABA immunoreactivity following microinjections of the retrograde tracer into the lateral hypothalamus (Fig. 14).

The results of this study, coupled with the data described above, account for the differential effects of medial amygdaloid stimulation on defensive rage and predatory attack. In summary, the medial amygdaloid facilitation of defensive rage is mediated through a monosynaptic, SP pathway directly upon the medial hypothalamus, where integration of this form of aggression occurs. The suppressive effects of the medial amygdala upon predatory attack are mediated over a disynaptic pathway. The first limb of this pathway constitutes the (excitatory) SP projection from the medial amygdala to medial hypothalamus, and the second limb consists of a GABAergic projection from the medial to lateral hypothalamus whose functions are mediated by

GABA_A receptors in the lateral hypothalamus, where integration of predatory attack occurs.

Most recently, a study [55] using a retrograde tracer and immunocytochemical labeling for GABA showed that the inhibitory projection from medial to lateral hypothalamus is matched by a reciprocal GABAergic projection from lateral to medial hypothalamus. This study also found that bicuculline antagonism in the medial hypothalamus did not facilitate defensive rage elicited by medial hypothalamic stimulation alone; however, bicuculline blocked the suppressive effects of lateral hypothalamic stimulation upon defensive rage elicited by stimulation of the medial hypothalamus. The overall findings of these studies are summarized in Fig. 10.

The discovery of these reciprocal inhibitory pathways gives a neuroanatomical basis for the longstanding observation that manipulations that inhibit defensive rage will also facilitate predatory attack, and vice versa. For example, Adamec [2–6] and Adamec and Stark-Adamec [7] observed that limbic kindling involved, in part, neurons of origin of the stria terminalis, a tract which carries fibers from the amygdala to medial hypothalamus. Kindling of these sites caused changes in the behavioral repertoire of the cats—specifically, they became more defensive and less prone to display predatory responses. If this kindling directly facilitated neuronal activity within the medial hypothalamus as a result of activation of the stria terminalis, then such excitation would have enhanced functions associated with the medial hypothalamus, such as defensive behavior. Congruently, the observed reduction in predatory responses may have been due to inhibition of the lateral hypothalamus by activation of the short GABAergic projection from the medial hypothalamus.

3.8.3. GABA in the rat

Adams et al. [9] and Roeling et al. [174] gave evidence for involvement of GABA receptors in hypothalamic aggression in rats. Local infusion of the GABA_A antagonist bicuculline induced attacks, [174], and the GABA antagonist picrotoxin also induced aggression [9]. Most recently Haller et al. [91] elicited aggression in the hypothalamus with a mixture of glutamate agonist and bicuculline applied by microdialysis, but this mixture seemed to work only in experienced fighters.

3.9. Effects of administration of tranquilizers, antidepressants and psychotropic drugs upon stimulation-induced aggressive reactions

A number of investigators have attempted to determine how tranquilizers, antidepressants and psychotropic drugs affect the aggression elicited by brain stimulation, using various strategies and objectives. In one approach, aggressive behavior is measured as part of a battery of behavioral and physiological tests in order to assess the efficacy of a number of different compounds. In this situation, the

principal concern is to characterize the properties of the drugs for purposes of clinical applications. In a second approach, drugs are employed as tools in order to study how specific transmitters affect aggression. In general, when positive results are obtained from drug tests, the drugs are likely to appear to *suppress* aggression. The primary difficulty in interpreting such results is that it may not be possible to determine whether such effects are behaviorally specific to aggression or extend to a wider range of behavioral (motor) responses; few studies have addressed this issue.

Early studies indicated that thresholds for defensive rage elicited from the medial hypothalamus of the cat are elevated following administration of antidepressants such as imipramine, desimpramine and amitriptyline [30, 79]. It should be noted that imipramine and desimpramine also attenuate predatory attack responses in the cat [69]. In particular, one study [68] observed that imipramine had little or no effect upon defensive rage in the cat and another [164] found differential dose effects: a low dose (2.5 mg/kg) facilitated defensive rage and a higher dose (8–10 mg/kg) suppressed this response. However, the clinically effective antidepressant fluvoxamine has significant effects on hypothalamic attack in the rat [112, 118, 158].

Considerable attention has been given to the benzodiazepine drugs, which act upon the GABA receptor complex. Investigators have utilized chlordiazepoxide in several species. In the rat [162], cat [28, 79, 137] and monkey [67], peripheral administration resulted in a suppression of defensive rage and fighting responses. However, in the rat, a study reported that chlordiazepoxide facilitated the occurrence of “quiet biting attack” in the rat [162], whereas another study reported that it affects lateral threat more than biting or fighting [118]. It appears that, in rat, benzodiazepines only have effects at the highest doses, where the muscle relaxant properties of these drugs are very pronounced (Table 2 and Ref. [118]).

Shaikh et al. [189] observed that carbamazepine selectively suppressed PAG-elicited defensive rage in cats while having no effect upon PAG-elicited predatory attack. By comparison, in rats, carbamazepine has no effect on hypothalamic attack [118]. Similar findings with respect to medial-hypothalamically elicited defensive rage were observed with diazepam, oxazepam [137], etizolam [78] and Y-7131, an experimental drug [215]. Suppressive effects upon defensive rage were also noted for such anti-anxiety drugs as chlorpromazine and pentobarbital [30, 134]. Thus, the overall effects of benzodiazepines upon cat defensive rage are inhibitory, paralleling the findings obtained with GABA agonists.

Recently, a series of papers offered an alternative approach to the study of benzodiazepines and aggression [2, 5, 6]. These studies showed that when the anxiogenic inverse benzodiazepine agonist FG-7142 (*N*-methyl- β -carboline 3 carboxamide), which is a β -carboline, is systemically administered to cats, defensive behavior was

generally increased, while predatory behavior was suppressed. Moreover, the effects of FG-7142 upon defensive behavior were reversed following administration of the benzodiazepine antagonist, flumazenil. An interesting feature of these studies was that they were able to show that FG-7142 enhanced the evoked potential in the medial hypothalamus resulting from basal amygdaloid stimulation. Assuming that this evoked potential was mediated over the stria terminalis, it is reasonable to assume that potentiation of this response by FG-7142 resulted from its actions upon medial and adjoining basal amygdaloid neurons which comprise the origin of the stria terminalis. Furthermore, the differential effects of FG-7142 upon defensive and predatory behavior can be understood in terms of the circuitry from the medial amygdala to the medial and lateral hypothalamus that was elaborated above. Said otherwise, if FG-7142 produces its effects by driving neurons that comprise the origins of the stria terminalis, then activation of these neurons would excite medial hypothalamic neurons, which would increase the likelihood of occurrence of defensive rage. At the same time, activation of medial hypothalamic neurons would, by virtue of a GABAergic interneuron, suppress lateral hypothalamic neurons that mediate predatory attack. Additional studies are required to identify the neurophysiological effects of FG-7142 treatment upon neurons in the medial and basal amygdala and medial and lateral hypothalamus.

Ethanol, which may act upon GABA receptors, has been reported to affect defensive rage oppositely to the benzodiazepines. Specifically, ethanol was shown to facilitate defensive rage and suppress predatory attack in cats (Ref. [182] reviewed in Ref. [207]).

4. Summary and conclusions

The major achievements of the research carried out to date have been to characterize the functional anatomy and pharmacology of the synaptic regions critical for the expression and modulation of aggressive responses. Of particular significance have been the studies in which selective agonists and antagonists were administered to specific receptor populations involved in the expression and modulation of aggression.

Although the anatomical relationships governing aggression in the rat have yet to be elucidated, existing data suggest the presence of similarities as well as differences between the rat and cat. One similarity is that for both species, the hypothalamus seems to be critical for the expression of aggressive responses; and the attack mechanism seems to be powerfully modulated by different nuclei of the amygdala. Also, emerging data suggest that, for both species, serotonergic mechanisms play an inhibitory role in the regulation of aggression. The two species differ with respect to the organization of the response systems.

Specifically, in the cat, two distinct descending pathways from the hypothalamus to the PAG and other parts of the brainstem mediate the expression of defensive rage and predatory attack. However, in the rat, such a medial-to-lateral distinction for separate response systems is not apparent. In addition, while the PAG is critical for the execution of aggression and defense in the cat, its role in rodent aggression is unclear.

That this research is relevant to human disorders is illustrated by the following examples. In humans, low serotonin has been implicated in violent murder and suicide [21, 44, 59–62, 181]. Moreover, recently a genetic trait in humans, associated with abnormal serotonin metabolism and personality disturbances including aggressive dyscontrol, has been described [47], and mimicked in mice in which the gene for monoamine oxidase A was knocked out [54]. Moreover, reuptake inhibitors of serotonin like clomipramine, fluoxetine and fluvoxamine are therapeutically effective in obsessive–compulsive disorders that escape control of the central mechanisms involved in the assessment of response appropriateness [168]. In addition, propranolol is effective in the control of pathological aggression [199], and oxazepam is more effective than chlordiazepoxide in reducing feelings of hostility in humans [127]. These pharmacological and functional parallels suggest that studying the ethology, physiology and pharmacology of hypothalamic responses may facilitate the understanding of the pathophysiology of human behavioral disorders.

From the data presented here, it would appear that the central mechanisms involved in aggression are species-specific to a great extent. Such species differences in aggression between a highly specialized carnivorous species (i.e. cat) and an opportunistic omnivorous species (i.e. rat) have been postulated on functional grounds in classical ethological studies [128].

In retrospect, although much data has been accumulated concerning the neurobiology of aggression over the past 25 years, an overall understanding of the nature of the neurotransmitters regulating aggression has still not been achieved. Our capacity to identify precisely specific transmitters at key synapses along the pathways associated with the expression or modulation of the attack responses has been limited by available methodologies as well as by deficits in our knowledge of the functional neuroanatomy of aggression. Examples of some of the technical limitations include: (1) the unavailability of highly selective receptor subtype agonists and antagonists that are required for appropriate testing of given transmitter systems; (2) lack of appropriate neuroanatomical tools to identify precisely the pathways as well as synaptic relationships governing the functional pathways in question; (3) our general lack of precision in measuring transmitter release at given synapses in association with the expression of a specific form of attack behavior.

On the positive side, some of these limitations are in the process of being overcome. Our ability to combine such

methods as more precise anterograde and retrograde tract tracing procedures with immunocytochemistry and neuropharmacology will ultimately provide us with a better means of verifying the nature of the transmitters as well as the origin and distribution of the pathways under investigation. Methods for measurement of transmitter release, such as *in vivo* microdialysis, should aid in clarifying the nature of the transmitters released at key synapses during the expression of an attack response. Likewise, *in situ* hybridization and other histochemical methods will further help to identify the properties of neurons and neurotransmitter receptors under investigation.

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