

Severe Reduction of Rat Defensive Behavior to a Predator by Discrete Hypothalamic Chemical Lesions

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ABSTRACT: Nonspecific lesion and stimulation methods have suggested that the hypothalamus is critical for the expression of defensive behavior, although the organization of neural circuits mediating such behavior is unclear. In the rat hypothalamus, we found that increased Fos levels were restricted to specific cell groups following presentation of a stimulus (predator) known to elicit partly innate defensive responses. The dorsal preammyllary nucleus showed the most striking increase in Fos levels, and cell body-specific chemical lesions therein virtually eliminated two major components of defensive behavior but increased exploratory behavior, suggesting that this caudal hypothalamic nucleus plays a critical role in the expression of behavioral responses sometimes critical for survival of the individual. We have previously shown that the Fos-responsive cell groups in the medial hypothalamus are interconnected in a neural system distinct from those mediating reproductive and ingestive behaviors. © 1997 Elsevier Science Inc.

KEY WORDS: Behavioral systems, Dorsal preammyllary nucleus, Fos, Hypothalamus, Motivation, Reproductive behavior.

INTRODUCTION

The innate ability to execute well-coordinated defensive behavior constitutes that part of an animal's behavioral repertoire designed to ameliorate environmental threats (e.g., a conspecific or a predator). The innate response to an environmental threat, such as exposure to a predator, is characterized by overt defensive behaviors (e.g., freezing and "circa-strike" responses, including vigorous escape attempts or jump attacks), analgesia, and autonomic arousal, thought to be coordinated by a defensive behavioral system [4,13].

The seminal work of Bard [2] and Hess and Brugger [18] led to the widely accepted view that the hypothalamus plays an especially important role in the expression of defensive behavior. In an elegant series of experiments with decorticate cats displaying "sham-rage" attacks, Bard localized the most critical area for the expression of defensive responses to the caudal half of the hypothalamus [2]. Hess and Brugger then stimulated electrically points throughout the diencephalon, and identified the perifornical region as a key site for eliciting integrated defensive responses [18]. More

recently, the hypothalamic zone from which defensive behavior can be elicited has been expanded to include the ventromedial nucleus and anterior hypothalamic area [12,14,22]. Although initial hypothalamic chemical stimulation experiments failed to elicit defensive responses [1], patterns of somatomotor and autonomic responses resembling the behavior of animals facing natural threats have now been obtained from a number of hypothalamic medial zone sites [34]. However, a great deal remains to be learned about the functional role of these centers, and about how they are integrated into neural systems or circuits subserving defensive responses.

In the present study, we first attempted to delineate hypothalamic structures involved in the integration of innate defensive responses by examining Fos immunoreactivity in the hypothalamus of rats displaying defensive behavior during an exposure to a cat, a natural predator. Of particular interest, these observations suggested for the first time that the dorsal preammyllary nucleus (PMd) may be an integral part of hypothalamic circuitry mediating the integration of behavioral responses to threatening stimuli in the environment. To investigate the specific role played by the PMd in the initiation of innate defensive responses, another series of experiments demonstrated that cell body-specific chemical lesions placed in this hypothalamic site dramatically reduce defensive responses during an exposure to a predator, suggesting that this caudal hypothalamic nucleus is essential for the expression of behavioral responses sometimes critical for survival of the individual.

MATERIALS AND METHODS

Animals

Adult male Wistar rats ($n = 20$), weighing about 250 g and obtained from the local breeding facilities, were used in the present study. The animals were kept under controlled temperature ($23 \pm 1^\circ\text{C}$) and illumination (12 h cycle) in the animal quarters, and had free access to water and standard laboratory diet (Purina). Conditions of animal housing and all experimental procedures were conducted under institutional guidelines, and in accordance with NIH guidelines on animal care.

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Study of Fos Immunoreactivity in Animals Exposed to a Predator

Each day for 1 week before the experimental procedure, 10 animals were individually housed, and handled repeatedly by the same investigator that conducted the behavioral test. To examine the pattern of hypothalamic activation during the display of innate defensive behavior, five animals were then placed individually for 10 min in a closed, wired-meshed compartment (70 × 16 × 30 cm) located inside a larger arena containing an adult male cat (3 kg). The other five animals served as controls; they were handled in the same way, but were not exposed to a cat. Experiments were performed between 0900 and 1100 h.

One hour after the test, each animal was deeply anesthetized with sodium pentobarbital (40 mg/kg, IP) and perfused transcardially with 150 ml of 0.9% NaCl followed by 800 ml of 4% paraformaldehyde in 0.1 M borate buffer (pH 9.5) at 4°C. The brains were removed and postfixed overnight at 4°C in the same fixative with 20% sucrose, and then frozen. Three series of 30 μm sections were cut in the frontal plane on a sliding microtome. One series was incubated for 48 h at 4°C in a polyclonal anti-Fos antiserum raised in rabbit (Ab-2, Oncogene Science—lot#2940701) at a dilution of 1:10,000. The primary antiserum was localized using a variation of the avidin–biotin complex system (ABC) [19]. In brief, the sections were incubated for 45 min at room temperature in a solution of biotinylated goat antirabbit IgG (Vector Labs), and then were placed in the mixed avidin–biotin–HRP complex solution for the same period of time. Vectastain Elite ABC Kits were used and the working solution of avidin–biotin–HRP complex was prepared by adding 90 μl of reagent A + 90 μl of reagent B to 10 ml of 0.02 M potassium phosphate-buffered saline (KPBS) at pH 7.4. The sections were recycled through the biotinylated antibody and avidin–biotin–HRP complex, and then processed for peroxidase histochemistry. The peroxidase complex was visualized by exposure for 10 min to a chromogen solution containing 0.02% 3,3'-diaminobenzidine tetrahydrochloride (DAB) with 0.3% nickel-ammonium sulfate in 0.05 M Tris-buffer (pH 7.6) followed by incubation for 10 min in chromogen solution with hydrogen peroxide (1:3000) to produce a blue-black product. The reaction was terminated by extensive washing in KPBS. Sections were mounted on gelatin-coated slides, and then dehydrated and coverslipped with DPX. An adjacent series of Nissl-stained sections was always prepared for cytoarchitectonic analysis. Anatomical nomenclature follows [36].

Ibotenic Acid Lesion Experiments

To investigate a specific role played by the PMd in the initiation of innate defensive responses, 10 adult male Wistar rats (220–250 g) were initially exposed for 15 min to a male cat (3 kg), as previously described, and videotape-recorded for behavioral analysis. On the following days, bilateral ibotenic acid lesions were aimed at the PMd ($n = 5$), and for control experiments at the adjacent mammillary nuclei ($n = 5$). Each animal was deeply anesthetized with sodium pentobarbital (40 mg/kg, IP), and bilateral deposits of 200 nl of a 1% ibotenic acid solution (Sigma) were made through a stereotaxically positioned glass micropipette (tip diameter 50 μm) by applying high-pressure pulses provided by a Picospritzer II (General Valve Co.). Stereotaxic coordinates for placing the micropipettes, according to the Paxinos and Watson stereotaxic atlas [25], were A = 4.8 mm anterior to the interaural plane, L = 0.5 mm from the midline, and V = 8.5 mm below the surface of the cortex, for the PMd; and A = 4.2, L = 0.5, and V = 8.8 for the medial mammillary nucleus. After 15 days, animals were reexposed to a cat for 15 min, and videotape-recorded. Following behavioral tests, animals were then deeply anesthetized

with sodium pentobarbital (40 mg/kg, IP) and perfused transcardially with 150 ml of 0.9% NaCl followed by 800 ml of 4% paraformaldehyde in 0.1 M Na phosphate buffer (pH 7.4). The brains were removed and postfixed overnight in the same fixative with 20% sucrose, and then frozen. A series of 30 μm-thick frozen sections was collected throughout the hypothalamus, and Nissl-stained for analysis of the lesion.

The different behavioral items observed during the 15 min exposure were encoded for both groups before and after the placement of the lesion from the video tapes, using a microcomputer-based technique. The encoder was blind to the location of the lesion. The data was processed for each animal and for each item in terms of frequency (cumulated incidence per session) and duration (cumulated duration per session). The following behavioral items were individually coded: Freezing: cessation of all observable movements except those associated with respiration. Escape responses: jump directed to the top of the test cage or vigorous running away from the predator. Exploration: locomotion, looking around, sniffing or digging oriented toward the wall or the floor of the test cage.

By using the Kolmogorov–Smirnov D statistical method [40], the goodness of fit testing of normality was determined for the values of cumulated time spent freezing and exploring, as well as incidence of escape responses, before and after the lesion for each experimental group. Duration of freezing and exploration, as well as incidence of escape responses were then individually subjected to a repeated-measures split plot ANOVA design [20], treating the two independent experimental groups (animals that received PMd lesions and control experiments) as one factor, and repeated measures (pre- and postlesion) as the second factor.

RESULTS

Analysis of Fos Immunoreactivity in Animals Exposed to a Predator

Animals not exposed to the predator displayed a substantial number of Fos immunoreactive (*Fosir*) neurons in the medial supramammillary nucleus, whereas only a very small number of immunoreactive cells were found in other parts of the hypothalamus, including the lateral preoptic and lateral hypothalamic areas, perisuprachiasmatic and retrochiasmatic regions, and anterior and dorsomedial nuclei.

As described by Blanchard et al. [4], direct exposure to the predator induced in the rat freezing responses (“postencounter defense”) as well as episodes of vigorous running and jumping (“circa-strike defense”), and, compared to control animals, these animals presented very clearly increased Fos immunoreactivity in several specific hypothalamic sites. Thus, at the preoptic level, many *Fosir* neurons were found in the lateral preoptic area, in addition to a somewhat lower number of labeled cells distributed through the anterodorsal and anteroventral preoptic nuclei, and undifferentiated parts of the medial preoptic area (Fig. 1A and B). Notably, only occasional labeled neurons were found within the boundaries of the medial preoptic nucleus.

A large number of *Fosir* neurons was observed at the anterior hypothalamic level, where most of the labeled cells were found in the anterior hypothalamic nucleus, retrochiasmatic area, and adjacent parts of the perifornical region of the lateral hypothalamic area (Figs. 1C and D, and 2A). Within the latter, it was observed that *Fosir* neurons were clustered in two distinct groups, one dorsal to the fornix at midrostrocaudal levels of the paraventricular nucleus, and the other ventral to the fornix, extending to the intermediate hypothalamic area, as delineated by Geeraedts et al. [15] (Fig. 1C and D). In addition, a few *Fosir* neurons were also found

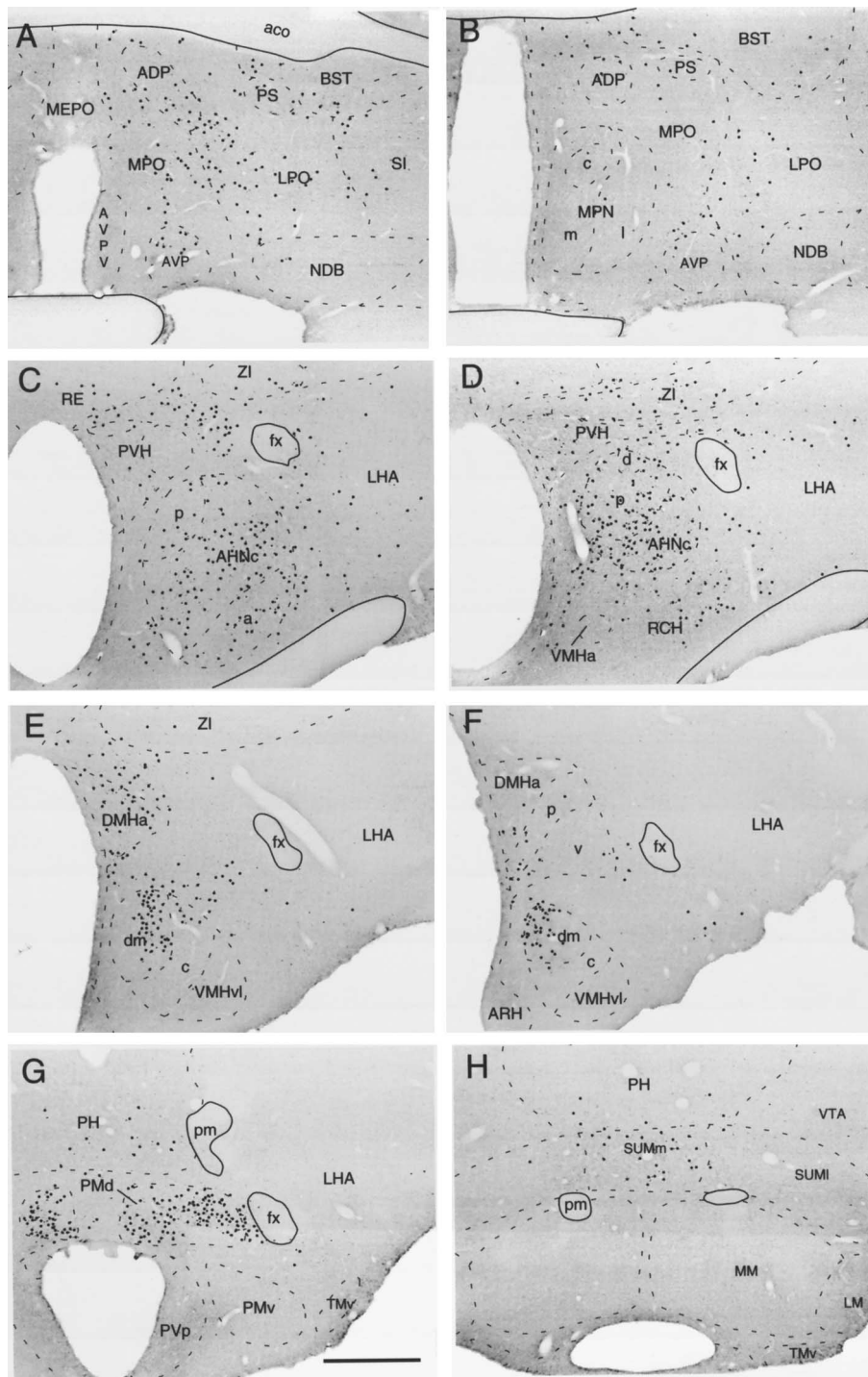


FIG. 1. Distribution of *Fosir* neurons in the rat hypothalamus after the display of defensive behavior. For visibility at this magnification ($\times 30$) location of labeled cells is indicated by black dots in a graphic overlay. Transverse sections from rostral (A) to caudal (H). Scale bar = 500 μm . Abbreviations used: ADP: anterodorsal preoptic n.; AHN_{a,c,d,p}: anterior hypothalamic n., anterior, central, dorsal, posterior parts; AM_v: anteromedial n. thalamus, ventral part; AR: androgen receptor; ARH: arcuate n.; AVP: anteroventral preoptic n.; AVPV: anteroventral periventricular n.; BST: bed n. stria terminalis; CUN: cuneiform n.; DM_{a,p,v}: dorsomedial n., anterior, posterior, ventral parts; ER: estrogen receptor; LHA: lateral hypothalamic a.; LHApf: lateral hypothalamic a., perifornical part; LM: lateral mammillary n.; LPO: lateral preoptic a.; MEPO: median preoptic n.; MM: medial mammillary n.; MPN_{c,l,m}: medial preoptic n., central, lateral, medial parts; MPO: medial preoptic a.; NDB: n. diagonal band; PAG: periaqueductal gray; PH: posterior hypothalamic n.; PM_{d,v}: dorsal, ventral premammillary n.; PS: parastrial n.; PVH: paraventricular n.; PVp: posterior periventricular n.; RCH: retrochiasmatic a.; RE: n. reuniens; RF: reticular formation; SC: superior colliculus; SI: substantia innominata; SNC_r: substantia nigra, compact, reticular parts; SUM_{l,m}: supramammillary n., lateral, medial parts; TM_v: tuberomammillary n., ventral part; TU: tuberal n.; VM_{a,c,d,m,vl}: ventromedial n., anterior, central, dorsomedial, ventrolateral parts; VTA: ventral tegmental a.; ZI: zona incerta; aco: anterior commissure, olfactory limb; fr: fasciculus retroflexus; fx: fornix; ml: medial lemniscus; pm: principal mammillary tract.

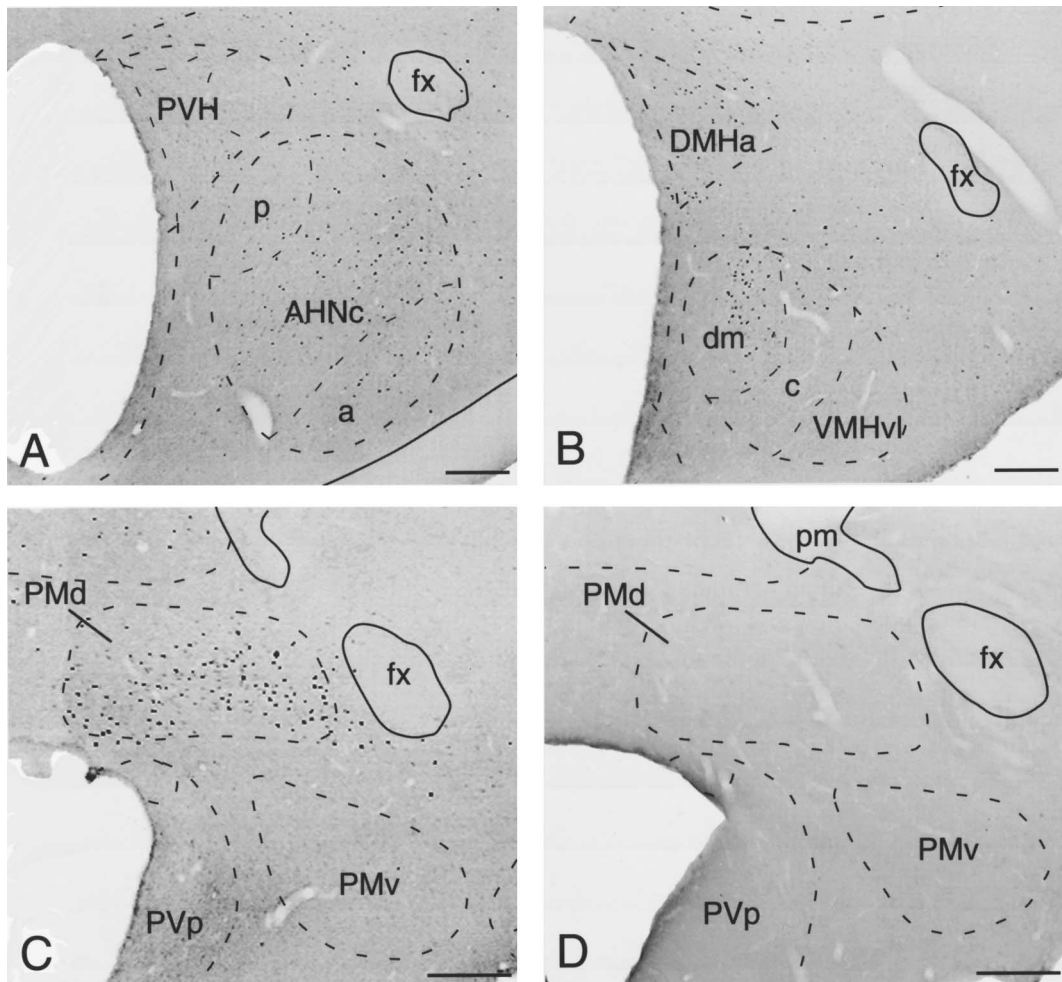


FIG. 2. Photomicrographs of transverse Fos-stained sections at the level of the AHN (A), VMH (B), and PMd (C) from an animal exposed to a cat; and at the level of the PMd from a control experiment (D). Scale bars = 200 μ m.

in other parts of the lateral hypothalamic area and in the paraventricular nucleus.

At the tuberal level, a dense cluster of *Fosir* neurons was observed in the dorsomedial part of the ventromedial nucleus, and substantial numbers of immunoreactive cells were also observed in the dorsomedial nucleus and in medial parts of the region between the ventromedial and dorsomedial nuclei (Figs. 1E and F, and 2B).

At the mammillary level, a strikingly dense population of immunoreactive neuronal nuclei were found throughout most of the dorsal pre mammillary nucleus—clearly one of the most highly activated hypothalamic regions during the expression of defensive responses (Figs. 1G and 2C). At this level, immunoreactive neurons were also found in the posterior hypothalamic nucleus and as in control animals, in the medial supramammillary nucleus as well (Fig. 1G and H).

In view of evidence that parts of the telencephalon and brainstem are also involved in defensive behavior (reviewed in [37]), it should be mentioned that a careful survey of the rest of the brain revealed very distinct increases in *Fosir* neurons in the cerebral cortex (infralimbic, prelimbic, anterior cingulate areas of the prefrontal region; secondary motor areas; lateral agranular retrosplenial area; and auditory and ventral temporal association areas),

septal region (rostral lateral and septofimbrial nuclei; and interfascicular and transverse nuclei of the bed nuclei of the stria terminalis), nucleus accumbens, thalamus (paraventricular, intralaminar, reuniens, and ventral anteromedial nuclei; lateral habenula), and brainstem (dorsal, dorsolateral, and caudal ventrolateral regions of the periaqueductal gray; superior colliculus; cuneiform nucleus; laterodorsal tegmental nucleus; and dorsal raphé). In the amygdala, a substantial number of *Fosir* cells was observed only in the medial nucleus (except for the posterodorsal part).

Ibotenic Acid Lesion Experiments

The parameters described above for ibotenic acid injections resulted in relatively small hypothalamic lesions, characterized by neuronal cell loss filled with gliosis (Fig. 3). In addition, as far as could be determined, none of our experiments showed detectable lesions in remote parts of the central nervous system, except for slight gliosis observed in some cases along the track of the micropipette. The animals recovered well from surgery and did not require any special care; the mean weight gain 15 days after surgery, when the animals were reexposed to the predator, did not differ significantly between the experimental groups (10.4 ± 1.4 g for animals with injections placed in the PMd vs. 10.6 ± 1.2 g for

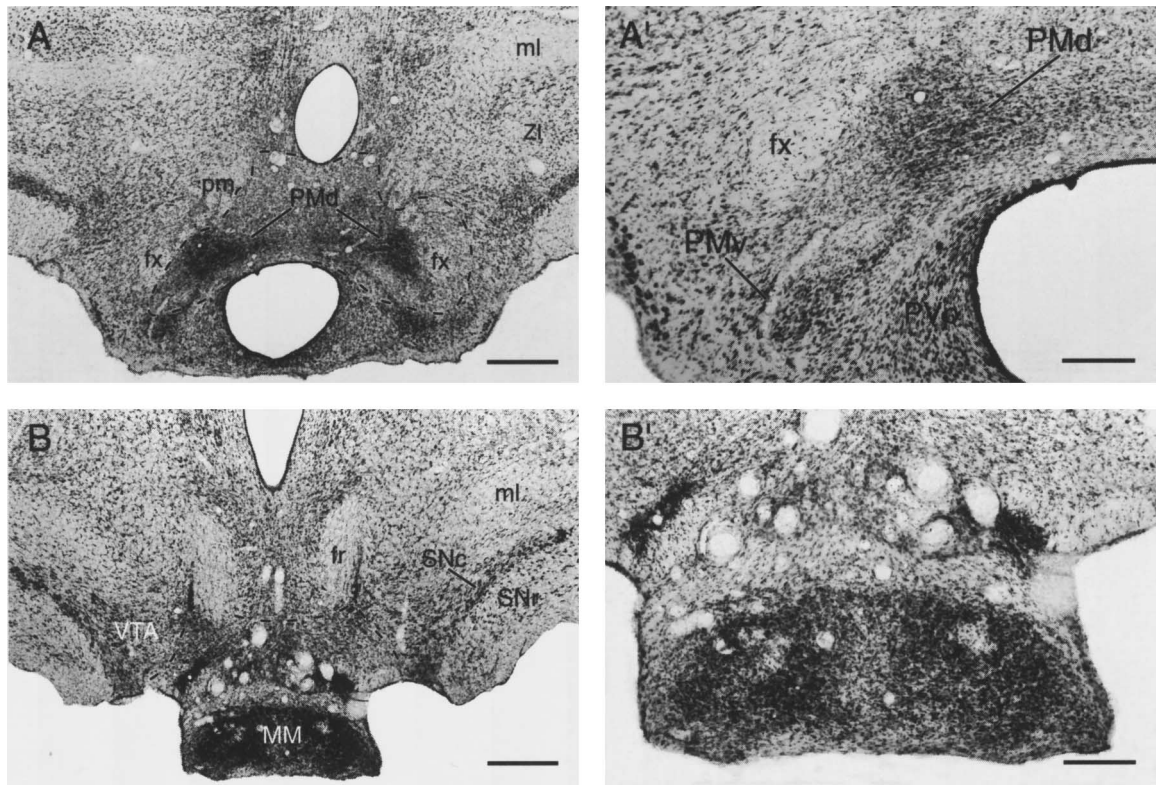


FIG. 3. (A, B) Low-power photomicrographs of transverse Nissl-stained sections through a bilateral ibotenic acid lesion centered in the PMd (A, experiment #9B) and in the medial mammillary nucleus (B, control lesion, experiment #6B), where the extent of the lesions are indicated by dotted lines. (A', B') High-power photomicrographs of the same sections shown in A and B, respectively, to illustrate the appearance of ibotenic acid lesions, characterized by neuronal cell loss filled with gliosis. Scale bars = 500 μ m in A and B; 200 μ m in A' and B'.

animals with injections placed in the medial mammillary nucleus; mean \pm SEM).

As shown in Fig. 4, the lesions in five animals were centered bilaterally in the PMd, and also spread to include part of the mammillary nuclei in four animals (medial mammillary nucleus—four animals, lateral mammillary nucleus—three animals, and supramammillary nucleus—two animals), the posterior hypothalamic nucleus in two animals, and the ventral pre-mammillary nucleus in two animals. In the other five animals, lesions were centered in the medial mammillary nucleus, with additional spread to the ventral tegmental area (two animals), posterior hypothalamic nucleus (one animal), supramammillary nucleus (three animals), and lateral mammillary nucleus (three animals).

As shown in Fig. 5, animals with bilateral PMd cytotoxic lesions presented a dramatic reduction in the incidence of escape and freezing responses compared to prelesion behavior and to animals with lesions just outside the PMd. Bilateral PMd lesions significantly reduced both measures, whereas in contrast the total time devoted to exploration more than doubled during exposure to the predator. There was an extremely significant *observation period* \times *lesion site* interaction for cumulated freezing, $F(1, 8) = 27.24$, $p < 0.001$, escape response incidence, $F(1, 8) = 14.7$, $p < 0.005$, and cumulated time spent exploring, $F(1, 8) = 35.18$, $p < 0.0005$, indicating that the effects observed after lesion placement depended on lesion site.

Although the day-to-day behavior of PMd-lesioned animals

(after recovering from surgery, and in the absence of a cat) has not been examined systematically, the most obvious qualitative difference as compared to other animals was their docility and paucity of vocalization when handled.

DISCUSSION

It has been shown that the hypothalamic medial zone is critical for the expression of defensive and reproductive behaviors [37]. In the medial zone, the anterior hypothalamic nucleus, dorsomedial part of the ventromedial nucleus, and dorsal pre-mammillary nucleus presented abundant *Fosir* neurons after the display of defensive behavioral responses. While previous studies indicate that the former two structures participate in the initiation of defensive responses [12,14,22], the present work examined a possible role for the dorsal pre-mammillary nucleus, and the results strongly indicate that it is also a critical hypothalamic site for eliciting innate defensive responses.

Our previous analysis of medial zone axonal projections with the *Phaseolus vulgaris*-leucogglutinin technique indicate that the anterior hypothalamic nucleus, dorsomedial part of the ventromedial nucleus, and dorsal pre-mammillary nucleus are highly interconnected; and that they are segregated from another medial zone circuit that includes the medial preoptic, ventrolateral part of the ventromedial, tuberal, and ventral pre-mammillary nuclei [6–8,27,35]. As revealed in the present study the former hypothalamic circuit is involved in integrating defensive behavior, and

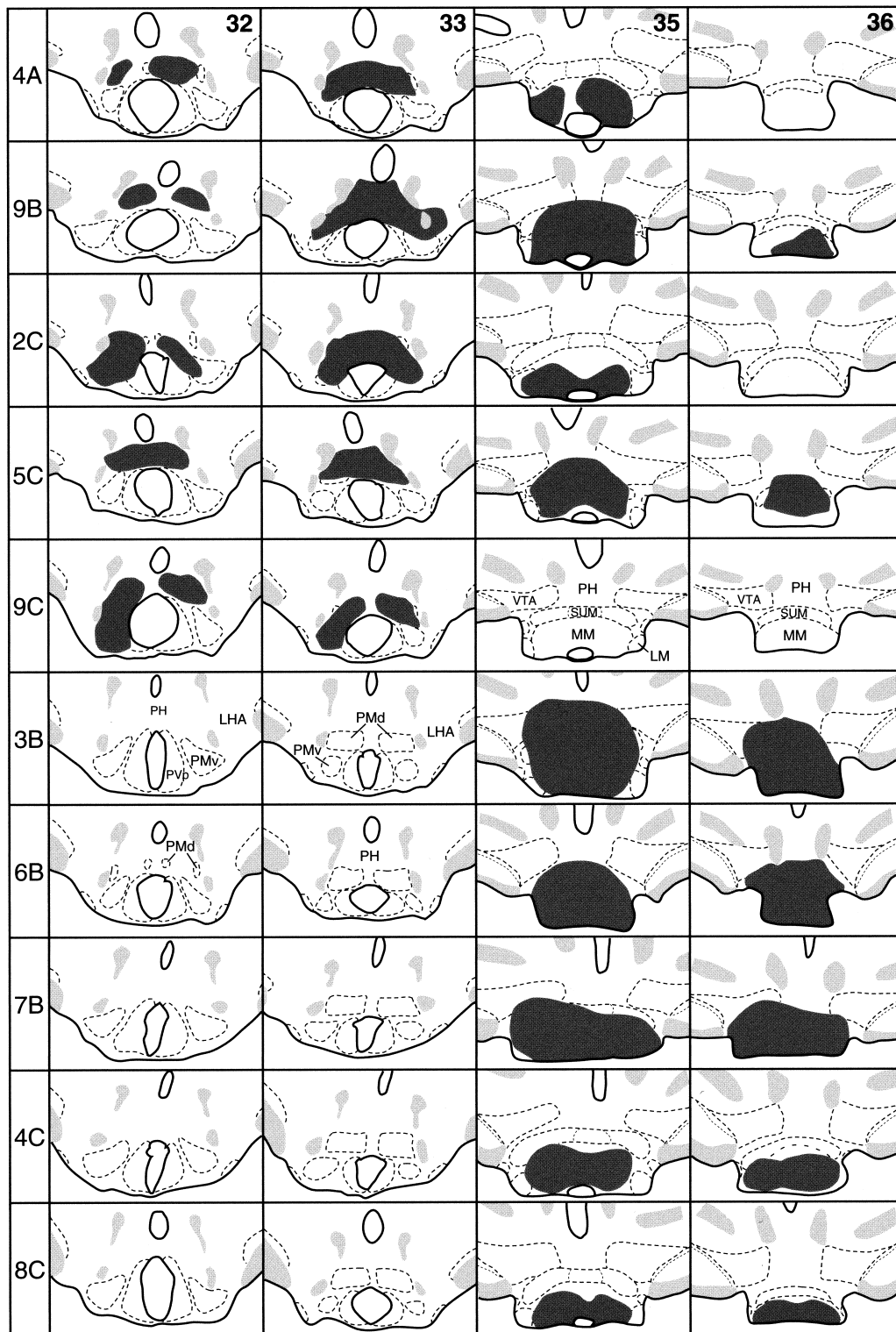


FIG. 4. Camera lucida plots to illustrate the extent of ibotenic acid lesions (dark gray areas) in the experiments where they are centered in the PMd (4A–9C), and in control experiments (3B–8C). The drawings for each experiment are arranged from rostral to caudal (left to right), and the number on the top of each vertical row indicates the approximate level of the section according to [36].

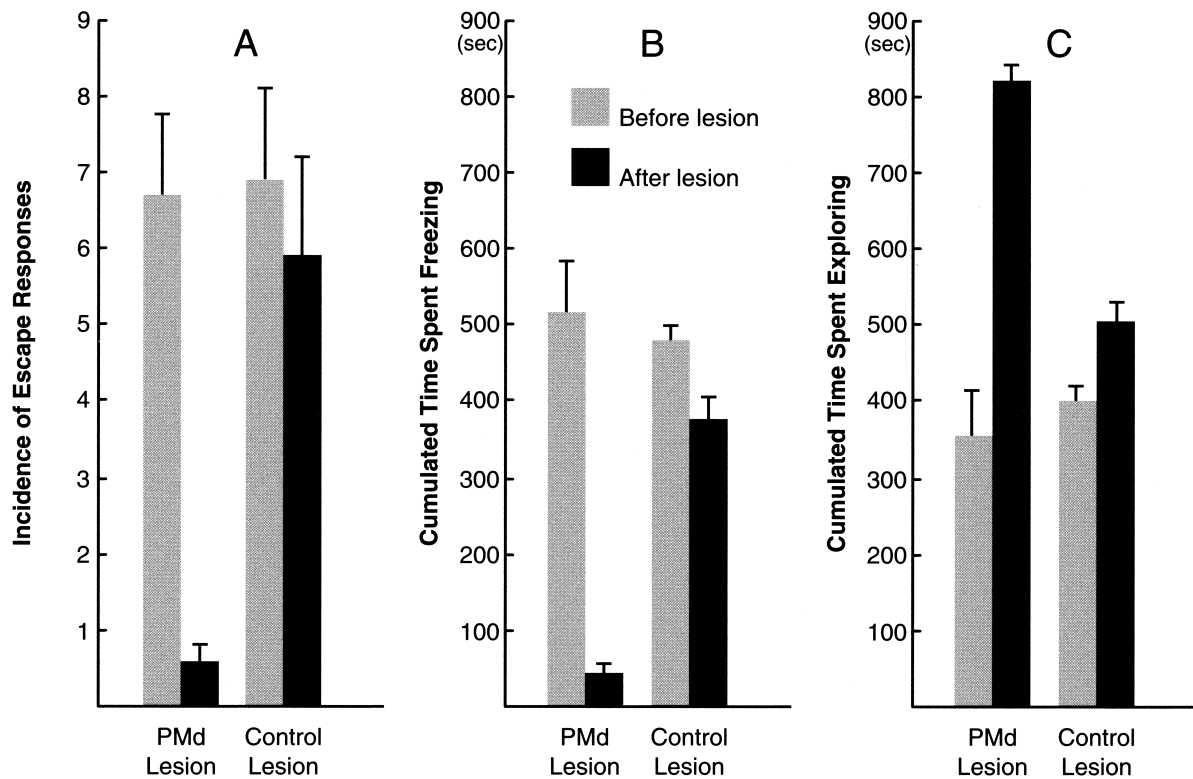


FIG. 5. Mean \pm S.E.M. incidence of escape responses (A), cumulated time spent freezing (expressed in seconds) (B), and cumulated time spent exploring (expressed in seconds) (C), during a 15-min exposure to a cat, for each experimental group before (open bars) and after (solid bars) placement of the lesions. $n = 5$, in all cases.

here it is important to note that elements of this circuit, such as the anterior hypothalamic nucleus and dorsomedial part of the ventromedial nucleus, receive direct input from certain telencephalic regions that displayed increased Fos immunoreactivity in our experiments, including the prefrontal region, lateral septal nucleus, and medial amygdalar nucleus [5,29,37].

In addition, many immunoreactive neurons were found in other parts of the hypothalamus, including the perifornical region, dorsomedial nucleus, lateral preoptic area, and medial supramammillary nucleus.

It is firmly established that integrated defensive responses occur with stimulation of the perifornical region [18,22,31], and two distinct zones within it were identified here. One lies just dorsal to the fornix at midrostrocaudal levels of the paraventricular nucleus and the other lies ventral to the fornix at about the same rostrocaudal level. It is worth noting that electrical or chemical stimulation of the latter region induces vigorous attack responses, and it has been included within the hypothalamic "attack area" [22,31]. Remarkably, both of these perifornical zones receive inputs from the medial zone nuclei activated during defensive behavior [6,8,27].

The dorsomedial nucleus, which also presented a substantial number of Fosir neurons in our experiments, is known to receive axonal projections from a wide range of hypothalamic medial zone nuclei [6–8,27,35], and in turn, projects massively to regions of the periventricular zone including the paraventricular and periventricular nuclei [39]. Thus, in the present context, activation of the dorsomedial nucleus suggests the modulation of visceral responses during defensive behavior.

Exposure to a predator also induced expression of Fos protein in neurons of the lateral preoptic area. It has been shown that both medial zone circuits mentioned above also project to the lateral preoptic area (see references above), which also receives substantial inputs from the nucleus accumbens [37,38] (which also displayed increased Fos immunoreactivity in our experiments). The lateral preoptic area, regarded as part of the subpallidal region [38], in turn, projects widely to other regions of the brain, including the cerebral cortex, reticular and mediodorsal thalamic nuclei, lateral habenula, lateral hypothalamic and ventral tegmental areas, pedunculopontine nucleus, periaqueductal gray, and superior colliculus [37,38]. Despite this complexity, functional evidence suggests that the subpallidal region participates in the modulation of somatomotor responses (especially locomotor behavior) and the general arousal associated with motivated behavior [37,38]. Thus, activation of the lateral preoptic area in the present experiments may reflect its role in general or nonspecific behavioral arousal.

Finally, both control and experimental animals displayed Fos immunoreactivity in the medial supramammillary nucleus, where exposure of animals to a novel environment (as here for both groups) has been shown to include *c-fos* expression [33].

To examine a possible role of the PMd in defensive behavior expression, bilateral ibotenic acid lesions were made, as were control chemical lesions placed in regions adjacent to the PMd that were occasionally damaged by injections centered in the PMd. Ibotenic acid lesions are known to kill neurons but largely spare axons passing through [17,32], and appear to have greater

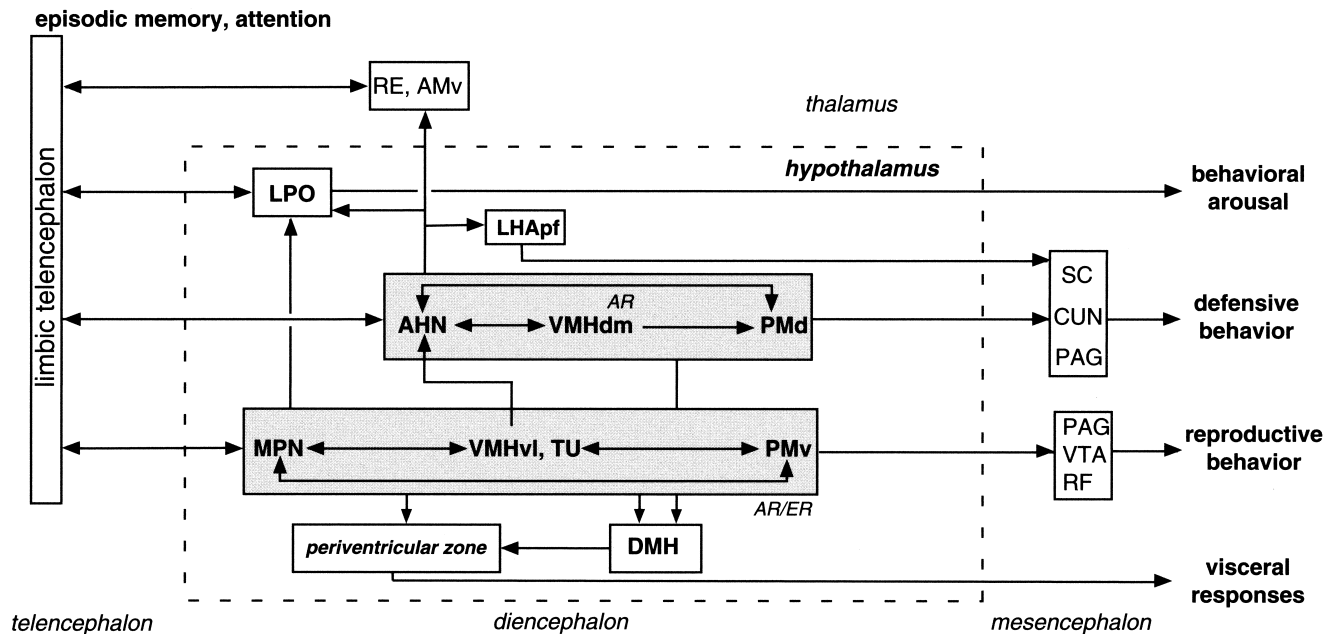


FIG. 6. A model of hypothalamic medial zone participation in two distinct though interrelated neural systems for defensive and reproductive behaviors. The two parts of the medial zone receive selective inputs from the telencephalon (left) and project to regions associated with visceral responses, arousal, attention, and memory; and specific aspects of sexual and defensive behaviors. Anatomical evidence for this model is reviewed in the text and [5–8,27–29,35,39].

neurotoxic effects on hypothalamic neurons compared to other amino acid neurotoxins, including *N*-methyl-D,L-aspartic acid, or quisqualic acid [17]. Our experiments with restricted hypothalamic ibotenic acid lesions strongly imply that neurons in the PMd are required for the adequate expression of at least two important components of defensive behavior—escape and freezing (attack itself was prevented by the wire screen). In addition, they suggest that lesions placed in the PMd do not grossly disrupt exploratory and ingestive behaviors, and other studies indicate that Fos is not upregulated in the PMd after exposure to other stressful situations, including forced swimming and immobilization [9,11]. Nevertheless, additional work is needed to determine whether PMd lesions interfere with the expression of other classes of behavior.

The PMd is known to receive massive bilateral inputs from the anterior hypothalamic nucleus, and also to a lesser extent from the dorsomedial part of the ventromedial nucleus [6,27]; and the PMd, in turn, generates a branched pathway that descends to the dorsolateral periaqueductal gray (which displayed increased Fos immunoreactivity in our experiments and is known to be critical for the expression of defensive behavior [13]), and ascends to the anterior thalamus [8]. Although the PMd projection to the dorsolateral periaqueductal gray appears to mediate freezing and escape components of defensive behavior, lesions in this part of the midbrain do not seem to influence conditioned fear responses [13], suggesting that the integrity of the PMd may not be critical for the expression of learned defensive responses. Furthermore, the central amygdalar nucleus, which is thought to be critical for the expression of certain conditioned fear responses [23], showed little increased Fos immunoreactivity in our experiments. Together, this evidence suggests that conditioned and innate defensive responses may utilize at least partly distinct neural substrates. Projections from the PMd to the ventral anteromedial thalamic nucleus and

then to the lateral retrosplenial area (with all three regions showing increased Fos immunoreactivity in our experiments) may be involved in modulating the eye and head movements associated with attentional mechanisms [28].

As mentioned above, four other hypothalamic medial zone nuclei, including the medial preoptic, ventrolateral part of the ventromedial, tuberal, and ventral premammillary nuclei, are highly interconnected, and form part of the sexually dimorphic circuit mediating reproductive behavior [6–8,27,35,37], and importantly they may upregulate Fos after sexual or parental behaviors [10,24,26,30]. Furthermore, yet a third interconnected hypothalamic system (not as closely associated with the medial zone) plays an essential role in ingestive behavior [37,39]. Thus, the organization of neural systems mediating three fundamental classes of motivated behavior is rapidly coming into focus, at least at the hypothalamic level (Fig. 6).

Clues about the role played by this hypothalamic circuitry in larger functional systems are provided by experiments involving mesencephalic and decorticate animals. Rats with complete transections between diencephalon and mesencephalon do not eat, drink, or reproduce, and their locomotor behavior is undirected; whereas, in contrast, decorticate animals display motivated, or goal-oriented, behavior in response to immediate needs, but not complex anticipatory behavior that involves foraging or exploration [3,16,21].

Together, the evidence suggests that hypothalamic networks (innate behavior generators) coordinate the output of appropriate somatic, autonomic, and neuroendocrine motor pattern generators, with corticohypothalamic pathways directing foraging behavior to specific goal-objects based on immediate perception of the environment; and based on anticipatory behavior, which involves planning and the use of episodic memory.

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