Amygdaloid lesion-induced obesity: relation to sexual behavior, olfaction, and the ventromedial hypothalamus

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Lesions of the amygdala have long been known to produce hyperphagia and obesity in cats, dogs, and monkeys, but only recently have studies with rats determined that the effective site is the posterodorsal amygdala (PDA)—the posterodorsal medial amygdaloid nucleus and the intramygdaloid bed nucleus of the stria terminalis. There is a sex difference; female rats with PDA lesions display greater weight gain than male rats. In the brains of female rats with obesity-inducing PDA lesions, there is a dense pattern of axonal degeneration in the capsule of the ventromedial hypothalamus (VMH) and other targets of the stria terminalis. Transections of the dorsal component of the stria terminalis also result in hyperphagia and obesity in female rats. Similar to rats with VMH lesions, rats with PDA lesions are hyperinsulinemic during food restriction and greatly prefer high-carbohydrate diets. The PDA is also a critical site for some aspects of rodent sexual behavior, particularly those that depend on olfaction, and the pattern of degeneration observed after obesity-inducing PDA lesions is remarkably parallel to the circuit that has been proposed to mediate sexual behavior. Medial amygdaloid lesions disrupt the normal feeding pattern and result in impaired responses to caloric challenges, and there is evidence that these behavioral changes are also due to a disruption of olfactory input. With its input from the olfactory bulbs and connections to the VMH, the PDA may be a nodal point at which olfactory and neuroendocrine stimuli are integrated to affect feeding behavior.

OVEREATING AND OBESITY have been studied with the use of several experimental animal models, including dietary, genetic, and brain-ablation models. Historically, the latter has been studied most extensively and has focused primarily on hypothalamic nuclei. However, the first published study of brain ablation-induced hyperphagia in animals did not target the hypothalamus [the first real report of hypothalamic hyperphagia and obesity was by Bailey and Bremer (8) in 1921] but instead focused on the temporal lobes. In 1888, Brown and Schäfer (16) reported that temporal lobectomies resulted in “insatiable” appetites in two rhesus monkeys. The monkeys were described as devouring their food “greedily, the head being dipped into the dish, instead of the food being conveyed to the mouth by the hands in the way usual with monkeys” (p. 311) and “she crams until her cheek-pouches can hold no more” (p. 318).

Decades passed before anyone else pursued these intriguing observations, but after a flurry of studies with cats and dogs in the 1950s and 1960s that pinpointed the effects to the amygdala, subsequent studies with rats yielded mostly negative and conflicting results. This review traces the history of amygdaloid lesion-induced obesity studies and concludes with recent studies that explain the past contradictory results and show that with its considerable input from the olfactory system and reciprocal connections with the ventromedial hypothalamus (VMH), the medial amygdala is in a key position to influence feeding and body weight regulatory processes.

TEMPORAL LOBECTOMIES IN MONKEYS AND HUMANS

In their classic study of the temporal lobes in the 1930s, Klüver and Bucy (110) reported that lobectomized rhesus monkeys displayed exaggerated oral behaviors (i.e., examined all objects by mouth) and a tendency to eat foods that are usually not preferred by monkeys: “animal foods, such as bacon, liver sausage, boiled ham, boiled tongue, smoked whitefish, ground beef and broiled lamb chops” (p. 994). Klüver and Bucy did not initially look at total food intake and body weight, and only much later reported hyperphagia and obesity in a lobectomized animal (17). The monkey was described as having a “tremendous appetite.” Pribram and Bagshaw (178), in 1953, similarly reported that lobectomized rhesus monkeys and baboons would eat meat and other foods normally rejected by monkeys and would chew on food soaked in quinine “with gusto.” One male monkey doubled its preoperative daily food intake.

Shortly after Pribram and Bagshaw’s study, Terzian and Ore (215) reported that after bilateral temporal lobectomy, a 19-year-old boy exhibited “…insatiable appetite and ate at least as much as four normal persons. . . . He would . . . insistently ask for food at any hour. . . . [and would] eat everything voraciously

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without preference for any certain food, lick the dish incessantly, and after 15 min asked for more food” (p. 375). Similar behavior was reported for a 20-yr-old man who had “extensive relatively selective destruction of the temporal lobes resulting from viral encephalitis: ‘Hyperbulimia was prominent: he ingested virtually everything within reach, including the plastic wrapper from bread, cleaning pastes, ink, dog food, and feces” (Ref. 147, p. 56; see also Ref. 3).

STEREOTAXIC LESIONS OF THE AMYGDALA IN CATS, DOGS, MONKEYS, AND HUMANS

Temporal lobectomies, of course, remove much more than the amygdala and include the hippocampus and overlying cortex. Some of the first stereotaxic surgeries of the temporal lobes that targeted specific nuclei were done with cats. In 1957, Green et al. (64) reported that 14 male cats with electrolytic lesions of the amygdala and piriform cortex became hyperphagic and obese. One animal was described as eating “as much as three pounds of cat food at a single session” (p. 517). In the same year, Morgane and Kosman (152) reported that six female and three male cats with suction lesions of the amygdala became markedly hyperphagic and obese. In both studies the lesions were large, but the authors identified the center of damage as the junction of the basal and lateral nuclei (64, 153).

A third study reported hyperphagia and obesity in a cat (sex not specified) with lesions mainly of the lateral and cortical nuclei (225). On the other hand, Wood (228) reported marked hyperphagia in four of nine cats (sex not specified) given electrolytic amygdaloid lesions and identified the center of damage as the central and medial nuclei. Daily food intake quadrupled. Koikegami et al. (111) similarly reported hyperphagia and obesity in a female cat with lesions of the medial amygdala. In stark contrast to all of these studies, Anand and Brobeck (5) did not observe any change in food intake in cats with lesions of either the lateral amygdala or the central and medial nuclei, and Anand et al. (6) observed aphagia and hypophagia in cats with large amygdaloid lesions.

In 1957, Fuller et al. (54) observed that food intake doubled in the first 2 wk after large suction lesions of the piriform-amygdala-hippocampal complex in dogs. However, it was Fonberg’s work with dogs in the 1960s and early 1970s that initially convinced many researchers of a role for the amygdala in feeding behavior. Fonberg reported that lesions of the dorsomedial amygdala (central and medial nuclei) in male dogs produced aphagia and weight loss (e.g., Refs. 47, 48, 53), that lesions of the lateral and basolateral nuclei produced hyperphagia and obesity (e.g., Refs. 48, 49, 52), and that basolateral lesions reversed the effects of prior dorsomedial lesions (50–52). Similar results were reported by others in cats (142). Fonberg (52) proposed that these effects were mediated via the hypothalamus, where lesions of the lateral hypothalamus (LH) and VMH produced similar effects.

Rhesus monkeys with lesions aimed at the amygdala also were found to display hyperphagia and/or excessive weight gains (108, 109, 198) or a willingness to eat almost anything, including meat and feces (1, 222). Several groups reported hyperphagia (generally lasting a few months) in humans given amygdaloid lesions to relieve epileptic seizures or schizophrenia. The reported center of damage included the entire amygdala (194), basolateral nuclei (89), medial amygdala (90, 146, 159), and the base of the striatum terminalis (19).

LESION STUDIES WITH RATS

Initial studies with rats often used large lesions that destroyed all or most of the amygdala. The result was hypophagia and weight loss (e.g., Refs. 5, 26, 111, 179, 197, 207, 208). Subsequent studies that used smaller lesions to target specific amygdaloid nuclei reported inconsistent and conflicting results regarding daily food intake and body weight. Lesions of the basolateral and/or lateral nuclei were reported to cause weight gain (15, 56, 139), no change in body weight (45, 74, 82, 83, 122, 144, 174, 187, 192, 195), or weight loss (32). [Many other studies that examined the effects of basolateral lesions on feeding-related behaviors did not mention any abnormal change in food intake or body weight (e.g., Refs. 2, 18, 86, 112, 155, 156, 158, 184, 233).] Lesions of the corticomedial nuclei similarly were reported to result in weight gain (33, 66), weight loss (26, 187, 216), or no change in body weight (83, 120, 121, 123, 145, 188, 195, 201). Studies of the effects of lesions of the central nucleus were equally conflicting, reporting weight or fat gain (14, 138), weight loss (15, 25, 56, 216), or no change (24, 34, 84, 180, 195).

Although Fonberg (50, 52) had proposed that there was an excitatory feeding system in the amygdala, damage to which causes aphagia and weight loss, later work with rats demonstrated that long-term weight loss occurred only when there was additional damage to the adjacent globus pallidus and/or striatum (e.g., Refs. 34, 181). The hypophagia and weight losses were often accompanied by sensory-motor deficits, including excessive gnawing and spillage of food, and these are well-established effects of damage to the globus pallidus (e.g., Refs. 34, 140, 151). This was probably the case for Fonberg’s aphagia-inducing lesions in dogs as well (see Ref. 47, Fig. 4, p. 742, and Ref. 50, Fig. 6, p. 458). In rats, lesions confined to the amygdala do not result in hypophagia, weight loss, or sensory-motor deficits (e.g., Refs. 34, 181, 195).

Even for those studies that reported overeating and/or excessive weight gains, the increases generally were very small (14, 33, 56, 57, 66, 139). There were two exceptions. Box and Mogenson (15) reported that male rats with lesions in the posterior part of the amygdala (posterior part of the medial amygdala or posteroventral part of the basolateral nucleus) displayed moderate weight gains on a high-fat diet, but this was not found for lesions of the central nucleus, which resulted in weight loss (but see previous paragraph). On the other hand, Lénárd and colleagues observed that mean body weight in male rats with 6-hydroxydopamine lesions in the area of the central nucleus was 10–15% greater than that in control animals (138), but they found only a very small increase in body weight with lesions of the basolateral nuclei (139).

With the contradictory results reported for cats and dogs (with regard to the critical nuclei) and the generally negative or small and conflicting results with rats, interest in this area of research waned, and by the early 1990s, leading textbooks did not even mention the amygdala in the chapters on feeding behavior (e.g., Ref. 22).

In the 1990s, King and colleagues began to reexamine the effects of small lesions placed throughout the amygdala and
adjacent temporal lobe structures in female rats. Bilateral lesions centered in the posterodorsal amygdala (PDA) resulted in marked hyperphagia (usually lasting 10–15 days) and excessive weight gains (92, 99, 100, 105, 181). Female rats with PDA lesions fed a standard laboratory chow diet typically gained 50–80 g in 20 days (compared with typical weight changes of −10 to +15 g for control animals), with weight gains of 100 g occasionally being observed (92, 93, 95, 99, 100). The difference in weight from control animals was maintained long term (95). Lesions confined to the ventral hippocampus or amygdalohippocampal area did not affect daily food intake or body weight (92), nor did lesions of the anterior, basolateral, or corticomedial groups of amygdaloid nuclei when the lesions did not include the PDA (105).

Rollins and King (181) found that substantial weight gains were obtained with very small PDA lesions limited exclusively to the posterodorsal medial amygdaloid nucleus (MePD) and the intra-amygdaloid bed nucleus of the stria terminalis (BSTIA). Figure 1 provides diagrams and coronal sections of the relevant amygdaloïd nuclei, and Fig. 2 shows serial sections of small obesity-inducing lesions limited to the MePD and BSTIA. Larger lesions that were centered in the basolateral, central, or anterodorsal medial amygdaloid nuclei sometimes resulted in excessive weight gains, but only when the lesions extended into the PDA. Among rats with basolateral amygdaloïd lesions, for example, there was a strong relationship between the dorsal extent of the lesions and weight gain (see Ref. 181 for details). For the complete series of lesions that extended all the way to the center of the brain (e.g., Refs. 14, 15, 33, 56, 66, 103), there was a strong relationship between the dorsal extent of the lesions and weight gain (see Ref. 181, Fig. 3). With the use of the grid point counting method to determine lesion size and extent, a multiple regression analysis of four rats with unilateral lesions aimed at the PDA (see Ref. 94) revealed that damage to the MePD, BSTIA, and globus pallidus accounted for 97% of the variability in weight gain, with damage to the globus pallidus being negatively loaded in predicting weight gain (unpublished observation).

Injection of ibotenic acid into the PDA bilaterally has proven to be exceedingly difficult (because of the small size of the PDA, its location immediately adjacent to the lateral ventricle and globus pallidus, and widespread diffusion), but in two confirmed cases of bilateral PDA neuronal atrophy, there were excessive weight gains (Rollins BL and King BM, unpublished observation).

The BSTIA is just lateral to the MePD and is recognized by many researchers of amygdaloïd anatomy as a group of cells (immersed in fibers that are condensing to form the stria terminalis) between the central amygdaloid nucleus and the dorsal part of the medial nucleus (4, 126, 172). However, some other anatomists consider these cells to be part of the (ventral) capsular portion of the central nucleus (149, 212).

Analysis of the histological results presented in previous studies with cats and dogs in which hyperphagia and/or excessive weight gains were reported revealed that the successful lesions extended into the PDA (see Ref. 181 for details). For example, this was true for Green et al.’s basolateral lesions in cats (Ref. 64, Figs. 17 and 18, p. 543), Koikegami et al.’s medial amygdaloid lesion in a cat (Ref. 111, Fig. 1, p. 215), and Fonberg’s lateral lesions in dogs (Ref. 52, Fig. 5b, p. 73). The histological presentations in rat studies were often sketchy, but it is clear that in those studies in which hyperphagia and/or excessive weight gains were reported, the lesions were generally very posterior and/or very dorsal (e.g., Refs. 14, 15, 33, 56, 66, 139).

Rats with PDA lesions are hyperinsulinemic, even during food restriction (93), and display decreased uptake of leptin across the blood-brain barrier (9). They are not finicky eaters (103) but do not increase their food intake when their food is mixed with nonnutritive bulk and do not eat as much as control animals when they are allowed to eat for only 1 h per day (104). Rats with large lesions of the medial and central nuclei...
have an impaired feeding response to 2-deoxy-D-glucose (2-DG) (216), but it is not yet known whether this is true for rats with much smaller PDA lesions. Perhaps most notable is that rats with PDA lesions display a strong preference for carbohydrates over fat or protein (104). Even those animals that greatly prefer a high-fat diet before surgery switch to a high-carbohydrate diet within a day or two after lesions. Although it may not be as apparent in cats and dogs (e.g., Refs. 52, 64, 152), in rats there is also a notable sex difference after lesions, with females gaining more weight than males compared with their respective control groups (102).

NEUROIMAGING AND PHARMACOLOGICAL STUDIES

Several recent studies have found increased amygdaloid activity in human subjects [as measured by PET or functional MRI (fMRI)] to food-related stimuli (7, 88, 128, 154), tastes (164, 235), and odors (236). Differences in amygdaloid neuronal activity were found between obese and lean subjects in response to satiation (58). Because of limitations due to spatial and contrast resolution, these studies did not distinguish among the various amygdaloid nuclei. However, with the use of fMRI, O’Doherty et al. (163) observed increased activity to stimuli that signaled the impending delivery of glucose that was specifically located in the posterior dorsal amygdala. Gottfried et al. (61) observed decreased activity in the posterior amygdala to the devaluation of visual stimuli that predicted odors that were associated with food in an appetitive conditioning paradigm.

It was not until very recently that pharmacological studies of feeding behavior targeted the PDA specifically. The results are

Fig. 2. Four serial sections through the brains of 6 rats with small posterodorsal amygdala (PDA) lesions. The lesions were centered in the MePD and BSTIA and then fused with the lateral ventricle posteriorly. Note also that the lesions directly damaged the site at which axons come together to form the stria terminalis. Weight gains are presented at left of each series (A–F). [From Rollins and King (181).]
limited, but promising. Huang et al. (76) observed that diet-induced obese-prone mice had higher levels of 5-HT$_{2C}$ mRNA receptor expression in both the VMH and the PDA than obese-resistant or control mice. A role for VMH 5-HT receptors in feeding behavior is well established (e.g., Refs. 72, 134). It is of interest, then, that Coscina et al. (29) found that rats with PDA lesions have a greatly attenuated feeding response to administration of the 5-HT$_{1A}$ agonist 8-hydroxy-2(di-n-propylamino)tetratin into the dorsal raphe nucleus and that previous research by Coscina’s laboratory had ruled out the paraventricular hypothalamic nucleus (PVN) as the critical site for this feeding effect (46; see also Ref. 30). Parker et al. (169) also found that administration of the 5-HT receptor antagonist metergoline into the posterior amygdala elicited feeding in female rats and that the magnitude of that response was dependent on the stage of the estrous cycle, as well as the palatability of foods tested. The cannula tips were in the posterior basolateral nucleus but so close to the PDA that the latter area would probably also have been affected (see Ref. 169, Fig. 1, p. 703).

Huang et al. (75) also found that diet-induced obese-prone mice had higher levels of melanocortin-4 receptor mRNA expression in both the VMH and PDA than did control mice fed a low-fat diet. As with 5-HT, melanocortin-4 receptors have been shown to play a critically important role in the VMH’s regulation of feeding behavior (see Ref. 91). Dopamine receptor mRNA expression apparently was normal in both areas (77).

**ANATOMICAL AND FUNCTIONAL CONNECTION WITH THE VMH**

The VMH is an important nucleus in the regulation of food intake and body weight (see Ref. 91). It has a large population of glucose-responsive neurons that dynamically respond to blood glucose and lactate levels (e.g., Refs. 189, 206). Food intake decreases when proopiomelanocortin neurons originating in the arcuate nucleus of the hypothalamus activate VMH brain-derived neurotrophic factor (BDNF) neurons (227, 232). Mice that are deficient in the nuclear hormone receptor steroidogenic factor 1 (SF-1) display abnormal VMH cytoarchitecture and/or reduced levels of VMH BDNF and hyperphagia and obesity (e.g., Refs. 35, 217, 218). Lesions of the VMH result in marked hyperphagia and obesity in a variety of species, including humans (see Ref. 91). Similar to PDA lesions (102), there is a sex difference in weight gain in rats with VMH lesions (31, 97, 193, 204).

The studies by Huang and colleagues (75, 76) suggest that the PDA and VMH have related or interacting roles in feeding behavior. In fact, one of the major efferent projections from the medial amygdaloid nucleus is to the VMH via the stria terminalis (21, 38, 71, 125), and there are reciprocal connections from the VMH (20, 60, 94, 166). Analysis of anterograde degeneration by the amino-cupric-silver method in the brains of female rats with unilateral obesity-inducing PDA lesions revealed dense terminal degeneration in the lateral septum, shell area of the nucleus accumbens, ventral striatum, medial preoptic area and anterior hypothalamus, and particularly in the dorsal (precommissural) component of the stria terminalis, ipsilateral VMH, and ventral premammillary nucleus (94).

Figure 3 shows the dense pattern of degenerating fibers in the capsule of the VMH after bilateral PDA lesions, a classic indicator of damage to the dorsal component of the stria terminalis (see Ref. 38, Fig. 9, p. 156, and Ref. 71, Fig. 2B, p. 289). There was little to no degeneration in the LH or PVN. (The lack of degeneration in the posterolateral LH provides further evidence that the lesions did not damage the central amygdaloid nucleus.) When unilateral PDA lesions were given 20 days after obesity-inducing unilateral VMH lesions, additional excessive weight gains were observed only when the PDA lesions were contralateral to the VMH lesions (67). This suggests an ipsilateral inhibitory feeding pathway from the PDA to the VMH.

Results of earlier studies that examined the effects of stria terminalis transections on feeding behavior appeared not to support this conclusion. Three studies that transected the stria terminalis early in its journey, before it separates into dorsal and ventral components, reported no change in food intake or body weight (12, 15, 157). Transections of the ventral amygdalofugal pathway, the other major pathway from the amygdala to the hypothalamus, resulted in a slight weight loss (170). Two additional studies that looked at the effects of coronal knife cuts anterior to the VMH, which presumably should have transected fibers of the dorsal component of the stria terminalis to the VMH, also did not observe any change in food intake or body weight (199, 220). On the other hand, four other studies did observe hyperphagia and excessive weight gains in rats with coronal knife cuts anterior to the VMH (65, 167, 171, 209). However, none of these studies verified that the cuts had actually transected stria terminalis fibers terminating in the VMH.

King and colleagues (101, 182) attributed these results to the sex difference in hyperphagia and weight gain that is observed after PDA (102) and VMH lesions (31, 97, 193, 204). In all but one (199) of the studies in which no weight changes were observed, males were used, whereas in all of the studies that reported reliable weight increases, females were used. King et al. (101) observed hyperphagia and obesity in female rats with transections of the stria terminalis just as it exits the amygdala, as did Rollins et al. (182) in female (but not male) rats with lesions of the stria terminalis at its most dorsal point or with coronal knife cuts just anterior to the VMH (see Fig. 4). Transection of the stria terminalis after coronal knife cuts was verified with an amino-cupric-silver stain for degenerating fibers. There was no degeneration in the medial preoptic area, anterior hypothalamus, LH, or PVN, but the pattern of antero-
There are other routes to the hypothalamus by which the amygdala could possibly influence feeding behavior. Swanson and colleagues have traced indirect pathways from the medial amygdala to the VMH via the hippocampus, lateral septum, and/or various divisions of the bed nucleus of the stria terminals (40, 42, 173), as well as a direct pathway from the central nucleus to the LH (173) and an indirect pathway from the rhomboid nucleus of the bed nucleus of the stria terminals to the PVN (41). Lesions of the lateral septal area do, in fact, result in very modest hyperphagia and weight gains in female (but not male) rats (113, 205, 223). However, based on the pattern of degeneration after obesity-inducing PDA lesions (94) or coronal knife cuts anterior to the VMH (182) and the effects of combination VMH-PDA lesions (67), it appears that PDA lesion-induced obesity results mainly from interruption of the direct stria terminalis pathway from the PDA to the VMH. White and Fisher (224) found that electrical stimulation of the medial amygdala suppressed food intake in food-deprived rats and that the suppression was prevented by either transections of the stria terminalis or lesions of the VMH nuclei. Recently, it has been found that mice deficient in SF-1 display not only abnormal VMH cytoarchitecture but a complete loss of projections to the amygdala, as well (218).

Behavioral studies also have revealed several similarities between rats with PDA lesions and those with VMH lesions. Similar to rats with PDA (or medial amygdaloid) lesions, hypothalamic hyperphagic rats have elevated plasma insulin levels both when fed ad libitum and when food restricted (68; see Ref. 96 for full references), display a normal feeding response to injections of insulin but a delayed response to 2-DG (98, 106), do not increase their caloric intake when their diet is adulterated with nonnutritive bulk (141, 210, 214), and show a preference for high-carbohydrate diets in the first several days after surgery (200). The latter appears to be mediated by serotonergic pathways (e.g., Refs. 134, 161).

**RELATION TO SEXUAL BEHAVIOR**

In addition to its role in feeding behavior, the PDA is also a critical site for male sexual behavior. The MePD displays increased Fos immunoreactivity during male rat sexual behaviors (10, 62, 63, 81, 162, 177). Fos-immunoreactivity within the lateral MePD is highly associated with sexual satiety in
male rats and hamsters (27, 28, 168), whereas the medial MePD displays activity during earlier components of sexual stimulation such as odors from estrous females (28). Lesions of the medial amygdala severely impair sexual behavior in male rats (e.g., Refs. 37, 59, 70, 114, 116), especially the ability to achieve noncontact erection in the presence of an inaccessible estrous female (191). Smaller lesions limited to the PDA also impair noncontact erections and significantly reduce the preference for anesthetized (to eliminate auditory cues) estrous female rats over anestrous females in a two-choice paradigm (115, 116).

Much of the medial amygdala’s role in male sexual behavior is mediated by fibers that project to the medial preoptic area (39, 87). However, it is well established that the VMH is also a critical nucleus for female sexual behavior and a target of amygdaloid efferent projections (see Refs. 20, 173). Winans Newman (226) has hypothesized that the posterior amygdala, medial bed nucleus of the stria terminalis, lateral septal area, medial preoptic area, anterior hypothalamus, and VMH are broadly interconnected to form a circuit regulating social behaviors such as sexual behavior. The pattern of anterograde degeneration observed after obesity-inducing PDA lesions is remarkably parallel with the circuit proposed by Winans Newman for reproductive behavior, with the cell columns for feeding behavior perhaps lying just lateral to those for sexual behavior (see Ref. 94).

The comparison with the anatomy for sexual behavior is intended only to suggest some common underlying causes for lesion-induced feeding dysfunctions and is not meant to imply identical etiology. For example, the pathways between the PDA and hypothalamus regulating male sexual behavior are largely dopaminergic (e.g., Refs. 39, 87), whereas, as noted previously, the evidence to date suggests that the PDA–VMH feeding pathway may be serotonergic (29, 76, 169; see also Refs. 72, 134).

It should also be noted that the medial amygdala, bed nucleus of the stria terminalis, and VMH all have a high density of gonadal steroid receptors (124, 143, 175, 176, 211, 226, 231) and that the PDA has been found to be sexually dimorphic to substance P-immunoreactive innervation (148) and estrogen-regulated neuropeptide gene expression (202, 203). Estrogen acts on VMH receptors to reduce food intake and body weight (79, 221), and this may account, in part, for the sex difference in weight gains observed after VMH (31, 97, 193, 204), PDA (102), and stria terminalis lesions (182). [Studies with neonatal and weanling rats have implicated gonadal hormones and/or growth hormone in the sex difference in weight gain observed after VMH lesions (43, 85, 127), but it is unlikely that PDA lesion-induced obesity is due entirely to an alteration in gonadal hormones, because PDA lesion-induced obesity was found to be additive with ovariectomy-induced obesity (102) and obesity-inducing PDA lesions had little or no effect on the estrous cycle (102).]

**FUNCTION(S) OF THE PDA IN FEEDING BEHAVIOR**

Many researchers have proposed that the amygdala is critical for an organism to interpret the significance of stimuli. For example, it has been proposed that the amygdala is important “in the learning of associations between stimuli and reinforce-
Lesions of the corticomedial amygdala result in this same persistent nibbling pattern of feeding (133).

Recall also that rats with PDA lesions have an impaired response to caloric challenges (e.g., do not increase food intake when their diet is mixed with nonnutritive bulk) (104). This, too, is a characteristic of rats with olfactory bulbectomy (131, 136).

Le Magnen (135) found that rats transiently increase their food intake when an odorous material that had been added to the diet is suddenly removed, and there is some preliminary data indicating that food odors may inhibit food intake in humans as well (73). Although olfactory bulbectomy by itself ordinarily does not alter total daily food intake, Larue and Le Magnen (132) found that bulbectomy in obese static-phase VMH-lesioned rats produced additional excessive weight gain. They concluded “that olfactory cues are involved effectively as a limiting factor in the control of the daily intake at a constant and calorically adjusted level” (p. 513).

Olfactory bulbectomy in rats also results in long-term deficits in serotonergic functioning within the amygdala (219). Huang et al. (76) recently found that compared with obese-resistant mice, high-fat diet-induced obese-prone mice had not only significantly higher levels of 5-HT2C mRNA receptor expression in both the VMH nucleus and the PDA but also higher levels of 5-HT2A receptor mRNA expression in the olfactory nucleus. Other brain regions did not differ.

It should be noted that the deficits in male rodent sexual behavior observed after PDA lesions are believed to be the result of disruption of input primarily from the vomeronasal organ (87, 118), and it is more likely that if the olfactory system plays a major role in the PDA’s contribution to feeding behavior, it is via the main olfactory system. Humans do not have a functional vomeronasal organ (87), but hyperphagia is still observed after amygdalecтомy (19, 89, 90, 146, 159, 194).

Of course, the total picture is more complex than just olfactory input. King et al. (94) found that small retrograde tracer injections in the PDA resulted in dense cell labeling not only throughout the bed nucleus of the accessory olfactory tract, medial division of the extended amygdala, posterior basolateral nucleus, amygdalolimbocampal and amygdalopiriform transition areas, and VMH and ventral premammillary nuclei but also in the ventral subiculum, paraventricular and subparafascicular thalamic nuclei, lateral septal area, and parabrachial nucleus. Nevertheless, the research with the PDA and sexual behavior strongly suggests that with regard to function, the input of the olfactory system on the medial amygdala plays an important role in feeding behavior and needs to be more extensively explored.

**SUMMARY AND CONCLUSIONS**

Initial studies that looked at the effects of amygdaloid lesions on food intake in cats and dogs reported hyperphagia and obesity resulting from damage to several different groups of nuclei, including the basolateral and lateral nuclei (49, 50, 52, 54, 64, 142, 152, 153, 225) and medial and/or central nuclei (111, 228). These discrepant results could be accounted for by two possible explanations: either much of the amygdala is inhibitory for feeding behavior, or the lesions (which were often large) overlapped in some critical area. The different embryonic development of the basolateral complex vs. the medial/central nuclei (78), as well as the generally negative results observed in subsequent studies with rats (e.g.,Refs. 5, 24–26, 32, 34, 45, 74, 82–84, 111, 120–123, 144, 145, 174, 179, 180, 187, 188, 192, 195, 197, 201, 207, 208, 216), makes the first possibility unlikely. Although those rat studies that did report lesion-induced hyperphagia and/or obesity also differed widely in the reported targeted nuclei (14, 15, 33, 56, 57, 66, 138, 139), King and colleagues have demonstrated that the critical area in rats is in the most posterodorsal aspects of the amygdala (e.g., Refs. 92, 99, 100, 105, 181) and that some of the negative results may have been due to the use of male subjects. In rats, amygdaloid lesion-induced hyperphagia and obesity are much more prominent in females (102). Detailed histological descriptions were often missing, but in those studies that provided it, the hyperphagia-inducing lesions extended into the most posterior and/or dorsal aspects of the amygdala (cats: Refs. 64, 111, 152, 153, 228; dogs: see Ref. 52; rats: Ref. 14, 15, 33, 56, 66, 139).
Examination of anterograde degeneration after obesity-inducing PDA lesions led King et al. (94) to conclude that the PDA influences feeding behavior, in large part, by its connections with the VMH via the dorsal component of the stria terminalis. Hyperphagia and obesity were also observed in female rats after transections of the stria terminalis at three different locations between the amygdala and VMH (101, 182). A comparison of the pattern of anterograde degeneration after PDA lesions (94) and coronal knife cuts just anterior to the VMH (182) revealed that the only common nuclei with extensive degenerating fiber terminals were the (capsule of the) VMH, ventral premammillary nuclei, and lateral septal area (with light degeneration in the nucleus accumbens), and of these, the VMH is most prominently involved in feeding behavior (see Ref. 91). Examination of the effects of combination VMH-PDA lesions confirmed that the effects of PDA lesions on feeding behavior are mediated largely by the VMH (67).

If it is logical to assume that the function of a nucleus is strongly associated with its major afferent projections, then one would predict that the processing of olfactory information would play a major role in any function of the medial amygdala. This has been well established for the PDA’s role in sexual behavior (115–117, 190, 191, 230), and there is indirect evidence of olfactory involvement in the PDA’s role in feeding behavior as well (as indicated by altered meal patterns and impaired responses to caloric challenges) (131, 133, 136).

With its dense population of gonadal steroid hormones (143, 175, 176, 211, 226, 231), influence on insulin (93) and possibly leptin (9), plus strong reciprocal connections with the medial hypothalamus (20, 21, 38, 60, 71, 94, 125, 166), the PDA occupies a key position in which to modulate behavioral and neuroendocrine functions controlled by the VMH and other medial hypothalamic nuclei. This should be particularly true for behaviors affected by olfactory cues such as sexual behavior and feeding. Olfaction is a major component contributing to the sensory quality of foods. Therefore, future research must address how the olfactory bulb influences the medial amygdala in its contribution to the regulation of feeding behavior.

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