Front. Biol. 2011, 6(1): 82–85
DOI 10.1007/s11515-011-0950-z

REVIEW

Amygdala, an important regulator for food intake

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Abstract **Amygdala plays a critical role in the regulation of emotional behavior and food intake. Neuropeptides are short chains of amino acids secreted by neurons as intercellular messengers, which regulate different functions such as emotion, food intake, learning and memory. In this review, we summarize the recent progress on the regulation of food intake by amygadala, which is mediated by those neuropeptides known to be critical in the regulation of this process.**

Keywords amygdala, food intake, neuropeptide

Introduction

The amygdala is a complex structure involved in regulation for various behavioral activities and emotional reactions (LeDoux, 2007). Most importantly, amygdala plays a key role in the modulation of fear- and anxiety-related behaviors (Davis et al., 1997; LeDoux, 2000; Roozendaal et al., 1997). As is well known, energy needs is not the only factor determining food consumption, and feeding behavior can also be influenced by changes in emotion. On the other hand, lesions of amygdala, particularly the posterodorsal region, would cause obesity and enhance preference for a high carbohydrate diet in rats, even in which preferred to a high fat diet before sugery (King et al., 2003; King et al., 1998). The basolateral area complex (BLA) and central nucleus (CeA) which provide direct and indirect projections to hypothalamus, are important complexes of amygdalo-hypothalamic circuits (Petrovich et al., 2001). The limbic system including the hippocampus, the amygdala, and the hypothalamus are extensively interconnected with each other, which are involved in the regulation of feeding and emotional behavior (Carlini et al., 2004; Ahn and Phillips, 2002). As a result, we intend to summarize the regulating functions of amygdala in food intake in this review, specifically focusing on neuropeptides.

Amygdala and food reward

Food not only serves as energy supply, but also is implicated in reward value. Sometimes feeding behavior results from limbic system influences relayed in part via the amygdala, and other reward factors. Interestingly, food reward happens under different circumstances. For example, the presence of pathogenic microorganisms would result in avoiding of food consumption; On the other hand, rich nutrients in food could promote feeding action. Under food deprivation, self-stimulation-induced feeding is amplified (Margules and Olds, 1962). Moreover, the ability of food to induce conditioned place preference, or self-administration of food, is augmented with food restriction (Lepore et al., 1995; Jewett et al., 1995; Figlewicz et al., 2006).

The amygdala needs to interact with a number of cortical and subcortical structures to perform the reward-related functions, including the nucleus accumbens, the midbrain dopaminergic system, the basal forebrain cholinergic system, the orbitofrontal cortex and the anterior cingulate cortex (Baxter and Murray, 2002). It has been widely demonstrated that both the amygdala and the orbitofrontal cortex (OFC) play an important role in the brain’s reward circuitry Gottfried et al., 2003). The amygdala and the OFC are intimately interconnected (Ghashghaei and Barbas, 2002). To carry out their reward functions, they interact with other dopaminergic structures, including the striatum, the dopaminergic midbrain and the anterior cingulate cortex (Goldstein and Volkow, 2002). However, the exact function of the amygdala and OFC to reward processing are still to be further investigated.

Received September 29, 2010; accepted November 15, 2010

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Amygdala and neuropeptides

Prior studies have shown that neuropeptides in the amygdala can regulate fear and anxiety responses, and a number of neuropeptides have been demonstrated to alter food intake following microadministration into the amygdala.

Amygdala and neuropeptide Y

Neuropeptide Y (NPY), a 36 amino acid orexigenic peptide, is one of the most abundant and widely expressed neuropeptides within the central nervous system. This neuropeptide is distributed in the cerebral cortex, ventral and dorsal striatum, and limbic system, including the hypothalamus and amygdala (Heilig and Widerlöv, 1990). NPY is associated with numerous behaviors including feeding (Clark et al., 1984), anxiety (Britton et al., 2000) and depression (Jiménez-Vasquez et al., 2000).

NPY and NPY receptors play an important role in regulating the anxiolytic behavior. NPY mRNA levels in the amygdala are altered during restraint stress. Acute restraint stress induces a significant decrease in NPY mRNA, while repeated restraint (continued for 9–10 d) leads to an up-regulation of NPY mRNA in amygdala (Thorsell et al., 1998, 1999). The alteration of NPY expression in amygdala complex may be an adaptive response to different stress situation. Rats administered NPY (100 pmol) into the BLA showed significantly decreased anxiety behavior in social interaction (SI) test (Sajdyk et al., 1999). Intra-amygdala administration of NPY decreases anxiety-like behaviors in rats without altering the intake of standard chow diets (Heilig et al., 1993; Heinrichs et al., 1993), while in overnight-fasted rats, high fat diet intake and preference were selectively reduced without altering total caloric intake after intra-amygdala NPY administration (Primeaux et al., 2006). Since the anxiolytic effects of NPY are partly mediated by the amygdala, these effects may be due to the overall emotional condition of the animal. Therefore, it is possible that an NPY-induced decrease in anxiety is at least in part responsible for the NPY-induced decrease in fat intake (Primeaux et al., 2006). Further studies are needed to examine the possibility and to determine the underlying mechanism for this effect.

Amygdala and corticotrophin-releasing hormone

Corticotrophin-releasing hormone (CRH), a 41 amino-acid peptide, is released in the brain under stresses to integrate the endocrine, energy homeostasis, behavior, visceral, and autonomic responses. *In vivo* release of CRH in the central nucleus of the amygdala was notably upregulated by both stress exposure and food ingestion. In fact, the meal-elicited release of CRH was as great as that released by restraint stress within 20 min (Merali et al., 1998).

Two subtypes of high affinity receptors, CRH1 and CRH2, are expressed within the brain and mediate the cellular effects of CRH. Previous studies have demonstrated that systemic administration of CRH1 antagonists decreases ethanol self-administration in ethanol-dependent animals (Funk et al., 2007). Interestingly, studies have shown that CRH2 receptor subtype has an opposing function in mediating ethanol withdrawal-induced activities. For example, in ethanol withdrawal animals, the activation of CRH2 receptor decreases both the increased anxiety-like behaviors and ethanol self-administration (Funk and Koob, 2007).

Direct injections of CRH into the amygdala produce anxiety-like behaviors (Gray and Bingaman, 1996). There are large numbers of CRH-containing cell bodies and terminals in the CeA. Administration of CRH antagonist bilaterally into the CeA reverses the anxiety-like effects of ethanol withdrawal (Rassnick et al., 1993). The biological functions of CRH receptor activation in BLA are poorly understood, despite the fact that CRH receptors are more densely distributed in BLA than that in CeA. Infusion of CRH into BLA, but not CeA, reduces feeding. These effects are mediated by CRH1 receptor, but not CRH2 receptor. Behaviors after exposure to a stressor are identical to those recorded after intra-BLA CRH administration. It’s necessary and sufficient for eliciting stress-induced anorexia by the stimulation of intra-BLA CRH1 receptor (Jochman et al., 2005).

Amygdala and galanin

Galanin is a 29-amino acid neuropeptide with a C-terminal amide. Galanin and galanin receptors are widely distributed throughout cortical, limbic and midbrain areas, and take part in reward, learning, memory, pain, drinking and feeding regulation.

Intracerebroventricular administration of galanin induced a significant increase in c-Fos levels in dorsomedial hypothalamus and CeA. This finding confirms that galanin upregulates c-Fos activation in hypothalamic nuclei, and supports the role for galanin in central amygdala-modulated regulation of stress-responses and food intake.

Bilateral microinjection of galanin antagonist into CeA blocked the anxiolytic effect of yohimbine pretreatment before stress. Bilateral administration of galanin resulted in the anxiolytic effect (Khoshbouei et al., 2002). As to food intake, intra-amygdala administration of galanin increased food intake (Smith et al., 1996).

Amygdala and enterostatin

Enterostatin is an N-terminal pentapeptide, which is released from pancreatic procolipase by trypsin activity in small intestine (Erlanson-Albertsson, 1992). Enterostatin does not play an important role in the digestion of fat. However, it turned out to be an appetite-regulating peptide specifically against high-fat diet or fat, in comparision with carbohydrate or protein. Enterostatin was found to serve as a satiety signal with specificity for fat in rat and mouse. Since enterostatin and its precursor molecule procolipase were upregulated when fed a high-fat diet, it was suggested to serve as a negative feedback modulator during fat intake (Erlanson-Albertsson and York, 1997).

Specifically, enterostatin administration reduced fat intake when microinjected into the amygdala, as it did either by intracerebroventricular injection or given peripherally. It selectively inhibited fat intake and was the inhibited potency was greater when microinjected in the amygdala than in the PVN (paraventricular nucleus) (Lin and York, 1997). Serotonergic agonists administration into the PVN reduced fat intake and serotonergic antagonists attenuate the feeding reduction induced by amygdala enterostatin, suggesting that there were functional interactions between the PVN and amygdala, which affected the feeding response to enterostatin. After administration of enterostatin into the amygdala, the positive cells of c-fos were observed in the amygdala, PVN, lateral hypothalamus (LH), vertral medial hypothalamus (VMH) and arcuate nucleus (ARC) detected with immunohistochemistry. This result provided evidence that enterostatin activated amygdala neurons, which had functional and anatomic connections directly to the PVN and neurons in the arcuate, LH and VMH, which could innervate the PVN. Although there was significant c-Fos expression in neurons of the LH, ARC and VMH and PVN nuclei, the chemical phenotype of those neurons is not yet clear. An important further job is to summarize the characterization of the neurons in the areas showing activation of c-Fos. It will facilitate the study of the mechanism by which the amygdala enterostatin system induces the hypothalamic circuits (Lin and York, 2004).

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