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Overview of the central amygdala role in feeding behaviour

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Abstract

The neural regulation of feeding behaviour, as an essential factor for survival, is an important research area today. Feeding behaviour and other lifestyle habits play a major role in optimising health and obesity control. Feeding behaviour is physiologically controlled through processes associated with energy and nutrient needs. Different brain nuclei are involved in the neural regulation of feeding behaviours. Therefore, understanding the function of these brain nuclei helps develop feeding control methods. Among important brain nuclei, there is scant literature on the central amygdala (CeA) nucleus and feeding behaviour. The CeA is one of the critical brain regions that play a significant role in various physiological and behavioural responses, such as emotional states, reward processing, energy balance and feeding behaviour. It contains γ-aminobutyric acid neurons. Also, it is the major output region of the amygdaloidal complex. Moreover, the CeA is also involved in multiple molecular and biochemical factors and has extensive connections with other brain nuclei and their neurotransmitters, highlighting its role in feeding behaviour. This review aims to highlight the significance of the CeA nucleus on food consumption by its interaction with the performance of reward, digestive and emotional systems.

Key words: **Central amygdala: Feeding behaviour: GABAergic neurons**

Feeding behaviour and other lifestyle habits play a major role in health optimisation, obesity and metabolic disorder control[1]. The obesity crisis and obesity-associated diseases have heightened public health concerns in many societies[2,3]. Among more than 1 billion adults who are currently overweight worldwide, at least 300 million individuals are clinically diagnosed as obese. Obesity and being overweight pose a major risk of other chronic diseases[4].

Feeding behaviour refers to all habits related to receiving/consuming food and containing essential nutrients. Feeding behaviour is physiologically controlled through processes associated with energy and nutrient needs, such as appetitive, reward and fear behaviours as well as food consumption[5,6]. Food consumption is a highly complex survival. Different factors may participate in feeding regulation, such as neural response in several brain nuclei, hormonal signalling (of leptin, ghrelin, insulin and cortisol) and environmental factors[7]. Among these factors, the role of neural pathways and/or brain nuclei is more significant than other ones[7]. Regulating the feeding behaviour via neural changes has a major role in the maintenance of body energy balance. Recent research studies have recognised various neural circuits involving in homoeostatic feeding control. These circuits act in cooperation with the regulation of feeding[8]. Understanding those brain nuclei that are involved in feeding behaviour and their connections could be effective in developing and maintaining the treatments concerning the feeding disorders. Hence, identifying the brain nuclei cell types and their specific functions in the regulation of feeding behaviour is very significant for consciously choosing between the available clinical approaches.

Some studies have emphasised the major role of the hypothalamus and mesolimbic dopaminergic systems as key mediators in regulating food intake behaviour[9,10]. Nevertheless, the amygdala is seen as the main brain region with a critical role in feeding regulation[11]. The central amygdala (CeA) is a significant extra-hypothalamic region that has a determining impact on different physiological aspects and nutrition behaviours[12,13]. Several CeA inputs/outputs provide a vast connection surface for this core[14]. The CeA is also involved in different brain functions, such as regulating various emotional states (e.g. stress, fear, anxiety, pain and motivation), cognition, energy balance, reward system, food consumption and digestive

Abbreviations: BLA, basolateral amygdala; CeA, central amygdala; CeC, capsular part of the CeA; CeL, lateral part of the CeA; CeM, medial part of the CeA; CGRP, calcitonin-gene-related peptide; CRH, corticotropin-releasing hormone; GABA, γ-aminobutyric acid; LA, lateral amygdala; LPBN, lateral parabrachial nucleus; NPY, neuropeptide Y; Nts, neurotensin; NTS, nucleus tractus solitaries; PKC-δ+, protein kinase C-delta; Ppp1r1b+, protein phosphatase 1 regulatory subunit 1B+; PVN, paraventricular nucleus; Rspo2+, R-spondin2+.

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behaviour[15–27]. Because it is part of the amygdala–hypothalamic complex circuit, a significant role of the CeA in feeding behaviour is established, respectively, through direct and indirect projections from the brain stem and the paraventricular nucleus (PVN) of the hypothalamus[23,28,29]. Based on the results of previous studies, electrical lesions of the CeA could induce changes in feeding behaviour[24]. Petrovich *et al.* (2009) designed an experiment concerning the roles of CeA and basolateral amygdala (BLA) in associative learning. The CeA and BLA were bilaterally neurotoxic-lesioned in rats under an aversive cue that induced feeding cessation (presentation of a tone paired with foot shocks). When BLA-lesioned rats were presented with this aversive cue, they showed inhibition of eating. In contrast, CeA lesions in rats under the same protocol did not lead to a similar effect. Hence, the CeA, but not BLA, is crucial to controlling feeding by an aversive cue. An evidence has shown that CeA is an important nucleus in regulating feeding behaviour in aversive conditioning[24].

The CeA has extensive connections with other important brain centres that are involved in nutritional and reward systems, as well as intrinsic features of the nucleus. Therefore, the role of CeA compared with other brain regions in feeding regulation is more critical[8]. Also, since various types of information come together in the CeA (from the cortical region to the subcortical area, reward system and limbic system), the functions of this core are more distinctive than other brain regions[18]. The CeA acts as the major output nucleus of the amygdala[17]. Finally, the significance of CeA relates to different functions of the neurotransmitters and hormones involving in feeding behaviour[12,21,30–32]. Several brain nuclei participate in the regulation of feeding behaviour, and many studies have focused on identifying the neural mechanisms of food intake regulation[2,33]; however, the CeA is largely understudied. Therefore, this review aims to highlight the significance of the CeA nucleus in food consumption by investigating its interaction with various physiological systems, such as the reward, digestive and emotional ones.

The amygdala

The amygdala is a collection of cells located near the brain stem. As part of the brain's limbic system, it is located bilaterally in the medial temporal lobes of the brain[34]. Also, it is involved in different functions, including emotional processing, and has a pivotal role in memory-related, feeding and appetitive behaviours[23,27,34]. Even though at least thirteen different subnuclei compose this nucleus, the most clearly defined amygdala sub-nuclei are, respectively, the lateral (LA), BLA and central (CeA) nuclei of the amygdala[17,35]. The LA is the major site that receives inputs from visual, auditory and somatosensory (including pain) systems[7]. The BLA is critical for acquisition and expression of fear conditioning[7] as well as the control of emotional behaviours[36]. The neural circuits of BLA to CeA are important for appetitive behaviours[24] because different BLA neurons project to CeA neurons that mediate and/or suppress appetitive behaviours[21]. Accordingly, the CeA influences feeding mechanisms via multiple routes. Therefore, among all amygdala subdivisions, this core has the most significant role in regulating the feeding behaviour[16,19–21,23,24,27].

The central amygdala. The CeA is a striatal-like structure[18,35] and is involved in different functions relevant to food consumption, appetitive behaviours, energy balance and digestive behaviour[16,19–21,23,24,27]. Moreover, it also participates in non-feeding functions, such as fear, anxiety, pain, cognition, motivation and stress[15,17–20,22,23,25,26]. This nucleus includes lateral (CeL), capsular (CeC) and medial (CeM) subdivisions[18,21,35,37,38]. In Figure 1, several CeA subdivisions and neurons that are associated with food intake behaviour are illustrated[5,20,24,32,39–42].

The input/outputs of the central amygdala and their modulatory effects on food intake

The conductance-based model with a dynamical system for the CeA neural network represents the biophysical interpretation of an excitable cell in regulating the feeding behaviour[32]. The intra-connections and projections modulate feeding behaviour in the CeA[21] where there are direct and indirect connections with different hypothalamic nuclei[23,27,29]. Information is transferred to the CeA nucleus from multiple regions, such as the brain stem, diencephalon nuclei and limbic system[43]. Therefore, the CeA would connect to the brain stem areas that control the expression of innate behaviours and their associated physiological responses[44].

Inputs into the central amygdala

The numerous intra- and inter-connections between different amygdala nuclei provide inputs to the CeA[35]. For instance, the BLA affects the CeA through its protein phosphatase 1 regulatory subunit $1B^+$ ($Ppp1r1b^+$) parvocellular neurons and R-spondin2^+ ($Rspo2^+$) magnocellular neurons[21,26]. As represented in Fig. 1, the $Ppp1r1b^+$ and $Rspo2^+$ neurons provoke and inhibit appetitive behaviours which are normally regulated in the CeA[21]. However, the glutamatergic neurons in the LA and BLA have synapses with GABAergic neurons in the medial intercalated cells that are located between the BLA and CeA. It can be seen in Fig. 2 that these GABAergic medial intercalated cells connect the LA, BLA and CeA areas[17,35,37]. Also, the BLA and LA send glutamatergic outputs, respectively, to the CeL/M and CeL subdivisions of the amygdala[35,37]. In Fig. 2, the CeL and CeM make local inhibitory circuits together due to sending γ-aminobutyric acid (GABA) interneurons[35,37]. Hence, a distinct population of neurons in the CeA perform an opposing role in feeding[32]. The GABAergic protein kinase C-delta (PKC-δ^+) neurons in the CeL suppress feeding[25,32]. By contrast, the serotonin receptor 2a ($Htr2a^+$/PKC-δ^-) neurons in the CeL stimulate food intake[8,32,45]. The activation of PKC-δ^+ neurons in both CeC and CeL leads to the inhibition of appetitive behaviours. These two types of appetite suppression happened via threat stimuli and aversive tastes in the CeC, as well as through satiety in the CeL[21]. Also, BLA $Rspo2^+$ and calcitonin-gene-related peptide (CGRP) of the lateral parabrachial nucleus (LPBN) neurons would mediate food consumption via projecting to PKC-δ^+ neurons in the CeC; however, Kim *et al.* (2017) demonstrated that

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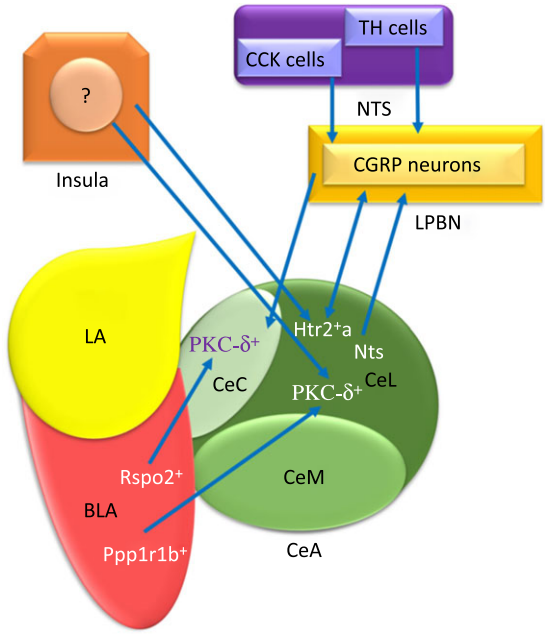

Fig. 1. The schematic organisation of information flow in the central amygdala (CeA) regarding feeding. Basolateral amygdala (BLA) affects the CeA with its protein phosphatase 1 regulatory subunit 1B$^+$ (Ppp1r1b$^+$) and R-spondin2$^+$ (Rspo2$^+$) neurons that may provoke and inhibit appetite, respectively. Insula modulates feeding behaviour via non-selective connections with both protein kinase C-delta (PKC-δ$^+$) and Serotonin receptor 2a$^+$ (Htr2a$^+$) neurons. The nucleus tractus solitarius (NTS) terminates food intake with glutamatergic input projections from the tyrosine hydroxylase (TH) and cholecystokinin (CCK) cells to PKC-δ$^+$ neurons of both lateral part of the CeA (CeL) and capsular part of the CeA (CeC) via activating the calcitonin-gene-related peptide (CGRP) lateral parabrachial nucleus (LPBN) neurons. Also, the BLA Ppp1r1b$^+$ neurons project into PKC-δ$^+$ neurons in CeL. In addition, the BLA Rspo2$^+$ and CGRP neurons of LPBN modulate appetite behaviour via projecting to PKC-δ$^+$ neurons in the CeC. LA, lateral amygdala; CeM, medial part of the CeA; Htr2a$^+$, Serotonin receptor 2a$^+$; Nts, Neurotensin. ⟶, Excitatory

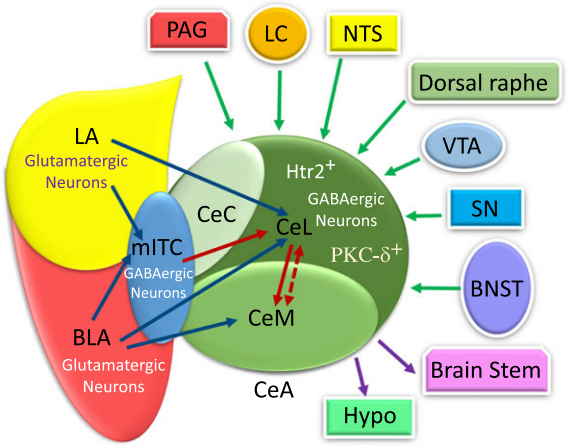

Fig. 2. The schematic illustration of internal and external input/outputs of the central amygdala (CeA). The lateral amygdala (LA) and basolateral amygdala (BLA) affect synapse on medial intercalated cells (mITC) (which is connected to the CeA) via their glutamatergic neurons. The CeA is composed of medial part of the CeA (CeM), capsular part of the CeA (CeC) and lateral part of the CeA (CeL) mostly with GABAergic neurons. The LA and BLA excite CeL and CeL/M, respectively, via glutamatergic projections. The CeA receives internal LA and BLA inputs in the amygdala circuits. Additionally, it receives information from multiple regions, such as the periaqueductal grey (PAG), locus coeruleus (LC), nucleus tracts solitaries (NTS), dorsal raphe, ventral tegmental area (VTA), substantia nigra (SN) and bed nucleus of the stria terminalis (BNST). Also, the CeA and mostly the CeM exert outputs to the brains tem and hypothalamus. PKC-δ$^+$, protein kinase C-delta$^+$; Htr2a$^+$, serotonin receptor 2a$^+$; PSTN, parasubthalamic nucleus; DMC, dorsal motor complex; Hypo: hypothalamus. ⟶, Input; ⟶, Output; ⟶, Excitatory; ⟶, Inhibitory; ⇢, Inhibitory Interneurons.

BLA Ppp1r1b$^+$ modulates appetitive behaviour via projecting to PKC-δ^+ neurons in the CeL[21]. As represented in Fig. 1, both CeL and CeM seem to promote reward-related behaviours by receiving inputs from the BLA Ppp1r1b$^+$[21].

Furthermore, the CeA receives a huge amount of information from multiple regions of the brain[8,35,46]. The sensory and cortical inputs come from the ventral tegmental area, locus coeruleus, nucleus tractus solitarius (NTS), periaqueductal grey, bed nucleus of the stria terminalis, parasubthalamic nucleus, substantia nigra and, finally, dorsal raphe nucleus[5,8,35,37] (Fig. 2).

The NTS terminates food intake with glutamatergic input projections from the tyrosine hydroxylase and cholecystokinin cells to the PKC-δ^+ neurons of both CeL and CeC; also, the NTS activates CGRP of the LPBN neurons[8,14,26,41,47–49]. Moreover, the CGRP receptors in PKC-δ^+ neurons are probably the aim of CGRP neurons in the LPBN[48,50]. However, Wang *et al.* (2019) indicated that the CGRP neurons in the LPBN suppress food consumption via excitatory projection to Htr2a$^+$ neurons in the CeA[45].

Satiety is the feeling of fullness and suppression of appetite and hunger. The satiety-related signals from LPBN projections excite PKC-δ^+ neurons in the CeA and mediate appetite by suppressing food intake[8,18,26,47]. Therefore, these signals mainly suppress appetite drive and create the feeling of satiety by releasing GABA from LPBN to PKC-δ^+ neurons in the CeA[18,41].

Another pathway for transporting food intake information is the insula-CeA connection[32]. The insula activates two opposite ways in modulating the feeding behaviour via non-selective connections with both PKC-δ^+ and Htr2a$^+$ neurons in the CeA[32]. Despite similar synaptic strength of the insula-CeA pathways in both PKC-δ^+ and Htr2a$^+$ neurons, food consumption behaviour will be decreased[32].

Outputs of the central amygdala

As illustrated in Fig. 2, the CeA has connections with almost all brain regions, such as the bed nucleus of the stria terminalis, lateral hypothalamus, PVN, ventral tegmental area, PBN, NTS, dorsal vagal complex and substantia nigra[8,13,37,51–54]. There are numerous projections from the CeA to different brain regions[8,13,31,37,52]. However, the CeM, unlike the CeL, seems to be more responsible for sending output projections to brain areas, such as the brain stem and hypothalamus[17,37]. Similarly, the CeL sends projection to different brain regions, including the preproglucagon neurons in the NTS[51], periaqueductal grey and PVN of the thalamus[55]. The terminal projections from CeC to the periaqueductal grey, PBN, NTS and ventromedial medulla have been observed too[14].

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Factors affecting the responsiveness of the central amygdala to food intake

Three main factors affect the responsiveness of the CeA to environmental parameters regarding the feeding behaviour; these factors could be categorised as receptors, neurotransmitters/neuropeptides and gene expression in the CeA[3,21,22,30,31,56]. These factors could increase and/or decrease food consumption (respectively, orexigenic and anorexigenic factors)[21].

The central amygdala and different receptors as well as neurotransmitters/neuropeptides

The CeA contains receptors that are related to food consumption[38]. There is evidence of opioid receptors containing kappa (κ) and mu (μ) receptors that mediated food consumption in the CeA[56,57]. Moreover, a unilateral opioid–opioid pathway from the CeA to PVN increased food intake via μ receptors[56]. The CeA contains GABA and glutamate receptors that act differently[3]. For instance, the direct injection of glutamate receptor agonist N-methyl-D-aspartate in the CeA increased food consumption[3].

Similar to various biochemical factors, different receptors could also exhibit different effects on food consumption by activating different CeA neurons[30,31]. A study has shown that direct injection of $GABA_A$ receptor agonist in the CeA decreased food consumption[3]. According to Anesten *et al.* (2019), the stimulation of glucagon-like peptide-1 receptors in the CeA nucleus reduces food intake[12]. Food consumption may be decreased by the microinjection of IL-6 into the CeA via the enhancement of glucagon-like peptide-1 receptors[12]. Moreover, Anderberg *et al.* (2014) demonstrated the anorectic effects of dopamine which are caused by the activation of the D_2 receptor in the CeA[39]. Furthermore, Pang *et al.* (2015) reported that secretin administration excited its receptors in the CeA. Also, the inhibitory effects of these receptors were mediated on food intake through the spontaneous electrical activity of GABAergic neurons and cAMP-protein kinase in the CeA[31]. According to some studies, approximately all neural populations of the CeA are GABAergic neurons[8,32,37,58]. The pituitary adenylate cyclase-activating peptide, which is a very important regulatory peptide in food consumption as well as its PAC1 receptors, all was highly expressed in the CeA[59]. Also, pituitary adenylate cyclase-activating peptide-induced anorexia and weight loss activate the local melanocortin and tropomyosin-related kinase receptor type B[59] (Fig. 3). Notably, orexin-A (a prominent neuropeptide in modulating food consumption) could mediate the orexigenic effects on the CeA via the OX1 receptors[30].

The central amygdala and gene expression

In previous studies on gene expression, it was reported that various genes were expressed in different CeA subdivisions that could have affected CeA functions in mediating feeding behaviour. The corticotropin-releasing hormone (CRH), Htr2a, neurotensin (Nts), dopamine receptor 2, PKC-δ, somatostatin and tachykinin 2 were expressed in the CeL, while calcitonin receptor-like, dopamine receptor 2 and PKC-δ were all expressed in the CeC[21,22]. However, electrophysiological studies have

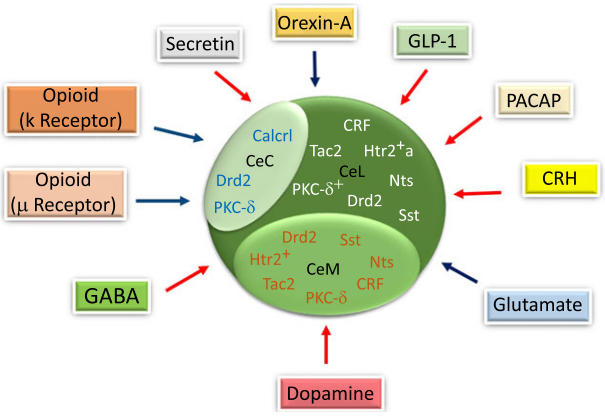

Fig. 3. The schematic diagram of gene expression in different parts of the central amygdala (CeA) and the effects of neurotransmitters/neuropeptides on food intake in the CeA. Corticotropin-releasing hormone (CRH), Tachykinin 2 (Tac2), serotonin receptor $2a^+$ ($Htr2a^+$), somatostatin (Sst), Protein kinase C-delta$^+$ ($PKC\text{-}\delta^+$) and neurotensin (Nts) are expressed in the lateral part of the CeA (CeL). The calcitonin receptor-like (Calcrl) and PKC-δ are expressed in the capsular part of the CeA (CeC). $Htr2^+$, Sst and Nts are expressed in the medial part of the CeA (CeM). Glucagon-like peptide-1 (GLP-1), pituitary adenylate cyclase-activating peptide (PACAP), CRH, dopamine, gamma-aminobutyric acid (GABA) and secretin decrease. Orexin-A, glutamate, μ and κ increase the food intake through their specific receptors in the CeA. Drd2, dopamine receptor 2. ⟶, Increase; ⟶, Decrease.

mostly documented PKC-δ^+ and $Htr2a^+$ neurons under a category of neurons with delayed firing patterns[5,32], yet, their roles were seen to be different in determining food intake behaviour[32] (Fig. 3). Also, it was indicated that Htr2a, Nts, somatostatin, CRF, PKC-δ, dopamine receptor 2 and tachykinin 2 were expressed in the CeM[21,22]. Finally, similar to other neurons, the electrophysiological characterisation of GABAergic neurons in the CeA depends on their specific gene expression[17,32]. Among these genes, CeL somatostatin, CRH, Nts, tachykinin 2, CeM Nts, somatostatin and tachykinin 2 provide an appetitive drive basis, while CeL PKC-δ would modulate appetitive behaviour negatively[21].

The central amygdala and different food intake modulation systems

The CeA is a critical brain region with significant roles in a variety of physiological and behavioural responses that are essential for survival, such as reward processing, digestion[30,41,52] and different emotional states like fear and stress conditions[8,20,27]. In the following sections, this review will elaborate on the role of the CeA in these responses.

The central amygdala and reward system

The brain's reward circuitry is one of the systems that are related to feeding behaviour[8]. This system includes various nuclei, such as the CeA, nucleus accumbens, midbrain dopaminergic system, cholinergic basal forebrain system, orbitofrontal cortex and anterior cingulate cortex[27]. Among these cores, the CeA not only has anatomical and electrical connections to different nuclei in the reward system but also reacts to motivational and emotional stimuli[28]. Hence, it plays an important role in

regulating food intake behaviour[18] and seems to be involved in food-seeking and appetite responses of the reward circuit as well. This might be due to its connection to the reward system, as well as the brain's gustatory and feeding centres[18].

Similarly, some studies have reported that the CeA circuits were activated with food-predictive cues (eating for hedonistic purposes or reward-associated reasons) via a population of the prepronociceptin-expressing cells in the CeA, which reinforce the rewarding properties of palatable food[41,60]. The prepronociceptin-expressing cells make a network of connections and projections to the ventral bed nucleus of the stria terminalis, PBN and NTS to process reward behaviours[41] and promote high-fat diet consumption that leads to obesity[41]. Even though they promote reward behaviour, their effects are not significant for the metabolism and energy homoeostasis[41]. Moreover, Torruella-Suárez *et al.* (2020) have reported the subset of Nts neurons in the CeA that lead to a hedonic consumption paradigm[61]. The Nts and Htr2a$^+$ make fundamental pathways neurons by projecting from the CeA to the PBN, respectively, in palatable drinking and eating patterns[61].

Overall, somatostatin and PKC-δ neurons in the CeL provide a basis for the correct response to the appropriate predictive cue (e.g. responding to the sweet water-predictive cue and not the bitterness-predictive one) via receiving excitatory inputs from the insular cortex[33,62]. However, in this continually changeable environment, predicting the consequent events is not an easy task[63]; the outcome of this cue will inevitably depend on the CeA interactions[63].

The central amygdala and digestive system

In previous studies, the anatomical evidence has supported the hypothesis regarding the reciprocal connections of the CeA with both NTS and dorsal vagal complex (two regions with neuromodulatory roles in gastric motility). Hence, the connections to the NTS and dorsal vagal complex make the CeA to operate as a gateway between them and the digestive system[30,64,65].

It is suggested that administration of orexin-A in the CeA could increase the gastrointestinal motility (for both contraction and emptying) through signals from the CeA to the dorsal motor nuclear complex and efferent activation of the vagus nerve (CeA–dorsal motor nucleus of the vagus–gastrointestinal tract axis)[30].

Following the intravenous injection of ghrelin, an increase of gastric acid secretion may happen in response to ghrelin via the excitation of the neurons in the CeA[52]. In this way, the projection of excited neurons from the CeA to the LPBN acts as a mediator that first excites the NTS and dorsal motor nucleus of the vagus (with direct innervation) and subsequently the neural system of the stomach[52]. The increase of gastric acid secretion was shown to have followed the gastrin injection and subsequently activated the expression of c-Fos protein in the CeA neurons[66]. Hence, CeA seems to act as a mediator between the nervous and endocrine systems in association with different brain areas from the brain stem to the cortex[23]. The relationship between CeA and other systems (e.g. the endocrine system) shows the importance of CeA in determining feeding behaviour. Therefore, this core facilitates the extensive connections between the brain, gastrointestinal tract and digestive hormones[30]. It is suggested to further investigate this perspective in future studies.

The central amygdala and different emotional states

Feeding behaviour and other lifestyle habits may considerably influence health and optimise obesity control in today's societies enduring various inconvenient emotional states[67,68]. Apart from eating essential nutrients for metabolic functions and energy requirements, feelings are key factors that may affect food consumption[27,60,69]. For example, stress can lead to overeating to relieve stress and relax, while severe stress can cause undereating[69]. Hence, the relevant CeA pathways, involved in feeding behaviour, would additionally be affected by different factors, such as emotional states like fear and stress[59].

Role of the central amygdala on food intake through fear. Fear experience may affect behavioural responses like food intake[70]. According to some studies, danger aversion and fear confrontation may suppress food intake[33,71]. The relationship observed between the CeA and the PVN of the thalamus mediates the appropriate behaviour in facing danger cue or food intake[33,71]. The LPBN neurons transfer the sense of danger to the CeA and activate PKC-δ^+ neurons that would suppress food intake[32,40]. The neural circuits through which PKC-δ^+ neurons exert their inhibitory influence on feeding should be further investigated[40]. Also, in other studies, encountering innate fear conditioning has inhibited the activation of the Htr2a$^+$ neurons in the CeA[8,70]. Although the notion of reduced food consumption by fear through the neural activation of PKC-δ^+ and inhibition of Htr2a$^+$ has previously been explored[8,70], the number of neurons participating in food intake reduction (through acute fear) remains unexplained so far[70].

Role of the central amygdala on food intake under stress and anxiety. Stress has become a common aspect of today's lifestyle[20]. As such, contradictory results have been observed regarding the stressors and food consumption level in various stress-related studies[20,72]. Stress-dependent eating often seems to happen under chronic stress situations[20]. Contrarily, food intake reduction and weight loss have been observed under sub-chronic psychological stress at different levels of intensity[68,73]. The sub-chronic administration of CRH into the PVN compared to its administration in the CeA increases food consumption earlier and more sharply[74]. As feeding-related CRH signalling in the CeA seems to act later than in the PVN, the CeA exhibits a stronger impact on the stress circuit and hypothalamic-pituitary-adrenal axis activation than on the food intake behaviour[74,75]. Moreover, the acute CRH injection into the CeA has been reported to reduce food intake[76]. However, a complex relationship between stress and eating pathways[20] is such that both stress exposure and eating could increase the CRH release in the CeA[16,28,69]. According to Petrovich *et al.* (2009), the CeA is an effective nucleus for the inhibition of food intake under chronic stress[24]. Nevertheless, the impact of CeA nucleus on food intake seems to be independent of the hypothalamic-pituitary-adrenal axis function[2].

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In addition, the relation between stress and food consumption is mechanistically complex[20]. Marlene *et al.* (2015) have shown that exposure to stress increased the glutamate level in the CeA[43]. Ip *et al.* (2019) demonstrated that stressful conditions enhanced food intake (especially, high-fat diet) by activating the neuropeptide Y (NPY) neurons in the CeA[20]. In the aforementioned study, NPY neurons in the CeA expressed insulin receptors; therefore, the consumption of a high-fat diet reduced the insulin responsiveness of these neurons in the CeA[20]. Furthermore, the NPY neurons in the CeA that were deprived of insulin receptors increased appetite and decreased energy expenditure under chronic stress[20,60]. Stress decreased the expression of insulin (acting as a negative feeding regulator) in the CeA[20]. Also, in the combination of stress and a high-fat diet, stress increased the appetite drive for overeating and overexpression of NPY[20]. Thus, the NPY level and its orexigenic effects seem to have enhanced the coping level to stress conditions[20,60]. It should be mentioned that an interaction between the NPY and Htr2a^{+} neurons in the CeA has been reported as well[20]. According to this study, activation of these receptors might reinforce the effects of food intake with positive valence.

All in all, anxiety, often associated with or triggered by a high level of stress, is defined by persistent, excessive ongoing worries even without the presence of any stressor[1]. In the state of anxiety, due to the anxiolytic impact of NPY in the amygdala, the intra-amygdala administration of this neuropeptide reduces the high-fat food intake without changing the total food intake[27,77]. Not only the presence of many NPY neurons and various NPY receptors in the amygdala but also the effects of NPY on other nutrition-related neuropeptides seem to be responsible for the occurrence of such behaviours[77]. Hence, exclusive research is necessary to better understand the influence of different emotional states over the roles of CeA regarding food consumption.

Conclusion

Food consumption consists of multiple behavioural sequences. The CeA plays a unique physiological role in various normal and abnormal emotional states, such as fear, anxiety and stress, the current review emphasised the importance of the CeA in understanding feeding behaviour. Notably, CeA is involved in various processes including the reward system and regulation of feeding behaviour. Finally, neuropsychological and behavioural studies have indicated the crucial role of the CeA in food consumption and modulating the behaviours related to the reward system.

Future directions

With the widespread prevalence of obesity and related metabolic disorders affecting the life quality and health system, the feeding circuits should be understood properly. Neuroscience may utilise the research studies regarding different brain nuclei for the development and maintenance of treatment methods for obesity and other related metabolic disorders. Hence, identifying the cell types and their specific functions in the CeA is critical for the regulation of feeding behaviour and emotional processing. Finally, understanding the proper feeding and its relevant disorders requires extensive research about the modulatory roles of the CeA on food intake mechanisms.

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