The Role Of The Lateral Hypothalamus In The Regulation Of Food Intake

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Abstract

Obesity is a fast and wide-spreading condition that continues to be a major global health problem. Body Mass Index (BMI) which is a person’s weight (Kg) divided by their height (m²) is used as a measure of obesity. An increase in BMI above the normal range increases an individual’s risk of mortality (1) and is also associated with an increased risk of developing number of co-morbidities such as coronary heart disease, type 2 diabetes mellitus and hypertension. Over the last century, the lateral hypothalamus (LH) has been implicated in the regulation of food intake but there is still uncertainty as to how it specifically affects it. To prevent obesity from becoming even more widespread, more research needs to be carried out to identify how the LH and other parts of the brain are regulating food intake.

At the start of the 20th century, Frölich discovered a link between pituitary tumours and obesity based on clinical observations in patients with Frölich’s Syndrome (pituitary tumours associated with excessive subcutaneous fat and hypogonadism). However, there was debate as to whether injury to the pituitary gland or to the hypothalamus situated above the pituitary was the cause of the syndrome.(2). A later study by Aschner in 1912 which was carried out in dogs showed that removal of the pituitary gland without damaging the hypothalamus situated above the pituitary was the cause of the syndrome.(2). A later study by Aschner in 1912 which was carried out in dogs showed that removal of the pituitary gland without damaging the hypothalamus did not result in obesity, implying that damage to the hypothalamus is related to obesity (3). A series of experiments were then conducted in rats in 1940 by Hetherington and Ranson which confirmed this idea. They placed bilateral electrolytic lesions in the hypothalamus of rats without disrupting the pituitary gland. The found that all of the rats that had widespread bilateral damage to the region occupied by the dorsomedial and ventromedial hypothalamic nuclei, the arcuate nucleus and the fornix had doubled their body weight and had an enormous increase of extractable body lipids. They also incidentally discovered that lesions in the LH lead to a decrease in food intake.(4). Consequently, another study was carried out, this time by Anand and Brobeck in 1951. They wanted to build on Hetherington and Ransons’ discoveries to localise which areas in the hypothalamus, when destroyed or lesioned, would lead to a reduction/complete inhibition of food intake (hypophagia) and also the areas that would lead to an increase in food intake (hyperphagia) and thus obesity. They placed well localised, electrolytic lesions in the hypothalamuses of Sprague-Dawley rats and found that lateral hypothalamic lesions lead to aphagia, adipsia, a loss of body weight, starvation and in some subjects, death.(5) These effects brought about by lesions in the LH were then collectively termed as a lateral hypothalamic syndrome and proved that the LH has a major role in regulating food intake. In 1954, Stellar summarised all of the previous findings; he lesioned the ventromedial hypothalamic nuclei (VMH) which caused an increase in food intake and when electrically stimulated, a decrease in food intake was the result. He also lesioned the LH, causing a decrease in food intake and when electrically stimulated, an increase in food intake resulted. From these observations, the conclusion was made that the VMH is the satiety centre and the LH is the feeding centre (6). Thus the ‘dual-centre’ hypothesis was formed and this was the dominant theory in explaining the regulation of food intake for many decades.

Naturally, the dual-centre hypothesis was challenged by many scientists over the following years. It was pointed out that the hypophagia caused by LH lesions was being caused by damage/interruption to the ascending nigrostriatal dopamine system passing in close proximity rather than to the LH itself. This resulted in a Parkinsonian syndrome and a significant reduction in nearly all movement and behaviour and hence a reduction in food intake (7)(8). It was observations like these that caused scientists to be uncertain
about the dual-centre model and the role of the LH in controlling food intake. Several years later, cell-specific lesion methods appeared, bringing the VMH and LH back into the spotlight. In a study conducted by Grossman in 1978, the LH was lesioned chemically with kainic acid without damage to the ascending dopaminergic system and resulted in hypophagia (9). This study reintroduced the idea that the LH was involved in feeding and was supported even further by neuroanatomical studies that displayed a lateral hypothalamic cell system which possessed direct projections to the cerebral cortex and to the autonomic and motor systems. The ascending and descending connections in this widespread lateral hypothalamic system predicted that it had the necessary anatomical range to support LH phagic function (10). This prediction was affirmed by the subsequent discovery of two new polypeptides in LH neurons; melanin concentrating hormone (MCH) (11) and the orexins (ORX) (12) which were found in separate, spatially overlapping neuronal populations in the perifornical region, LH area and zona incerta in the rodent and human brain (13).

Both of the ORX and MCH cell groups contribute to the entire range of LH neuronal projections, from the cerebral cortex to the spinal cord.(11,13). These peptides were found to have an orexigenic function which further implicated the LH in having a critical role in food intake. A study by Qu et al. about the role of MCH in the central regulation of feeding behaviour reported that MCH augmented ongoing feeding, fasting stimulated MCH gene expression in the hypothalamus and MCH mRNA was raised in genetically obese ob/ob (leptin deficient) mice (14). Transgenic mice overexpressing precursor MCH have also been shown to be hyperphagic and develop centripetal obesity (15).

ORX were discovered simultaneously by two groups of investigators, De Lecea et al.(16) and Sakurai et al.(12). It was initially observed that ORX’s effect on food intake were similar to that of MCH; it stimulated food intake when administered intracerebroventricularly (ICV) and its mRNA levels were increased by food deprivation (12). However, successive studies implied that the orexigenic effects of ORX were due to an increase in generalised behaviour arousal(17) as a deficiency in ORX or the ORX2 receptor in animals and humans is associated with narcolepsy(18,19). Even though the anatomical relationship between cells expressing MCH and ORX remained to be elucidated, there appeared to be at least two different signalling molecules which may be mediating LH-dependent food intake (13); MCH and ORX neurons may be regulating both cognitive and autonomic aspects of food intake (20).

Prior to and during the discovery of MCH and ORX, other major findings had been made in the field of food intake regulation. Scientists were moving away from the theory that specific hypothalamic nuclei controlled satiety and feeding. They were starting to believe that energy homeostasis was being controlled by neuronal circuit systems which signalled using specific neuropeptides. Intensive research was being carried out to identify orexigenic and anorectic neurotransmitters in the hypothalamus, followed by identification of the neuronal sites of their production, release and the receptors on which they acted upon. There was also evidence showing the relationship between these neurotransmitter producing neurons and the fact that these neurons could coproduce more than one appetite-regulating signal (21,22). Through this research it was discovered that there were two primary populations of neurons within the arcuate nucleus (ARC) which amalgamate signals of nutritional status and influence energy homeostasis. One neuronal circuit stimulates food intake through the expression of the orexigenic factors, neuropeptide Y (NPY) (13) and agouti-related protein (AgRP) (23), while the other circuit inhibits food intake via the expression of the anorectic neuropeptides, pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART)(24). In a study by Elias et al. it was found in rat and human models that the orexigenic MCH and ORX neurons in the LH comprise distinct populations that receive innervation from the NPY/AgRP and a-MSH (the POMC gene product)/CART fibres from the ARC (20). Therefore it is significant to note that peripheral circulating factors acting on the inhibitory and stimulatory neuronal feeding circuits in the ARC (through the blood-brain barrier) have an effect further downstream on the MCH and ORX neurons of the LH which project to the entire neuraxis, including monosynaptic projections to several regions of the cerebral cortex, to alter the regulation of food intake.

The position of the ARC in the brain is vital to its function; it is accessible to circulating signals of energy balance via the underlying median eminence as this part of the brain is not fully protected by the blood-brain barrier (25). Hence, peripheral signals (e.g. gut hormones, PYY and GLP-1) are able to cross the blood-brain barrier. This signifies the regulatory role of the blood-brain barrier in the passage of some circulating energy signals.

Possibly one of the most important discoveries with regards
to food intake and energy homeostasis in the last two decades has to be that of leptin. Leptin is a satiety hormone that suppresses food intake and decreases body weight. It is produced by white adipose tissue and plays a crucial role in the maintenance of neuroendocrine and body weight homeostasis. (26). It acts as a marker of adipose stores in the body; therefore the more obese an individual is the more circulating leptin they will have. Cloning of the leptin gene and demonstration that leptin administration to ob/ob (leptin deficient) mice corrects obesity as well as neuroendocrine and autonomic abnormalities observed proves that leptin is a vital factor in body weight homeostasis (27)(28). One of the sites of leptin action is the ARC, in particular the NPY neurons; they were found to contain leptin receptor mRNA (29) and leptin was also discovered to regulate levels of NPY mRNA; In a study by Stephens et al. it was found to inhibit the synthesis and release of NPY (30). POMC neurons within the ARC have also been shown to express leptin receptor mRNA (31) and as with NPY mRNA, leptin also regulates the level of POMC mRNA in the ARC; a study by Mizuno et al. demonstrated POMC mRNA expression is stimulated by leptin (32). It is important to note that NPY neurones are coexpressed with AgRP neurones. Therefore the effects that leptin has and the characteristics of leptin receptor expression on NPY neurones are also applicable to AgRP neurones. The significance of demonstrating the action of leptin on the orexigenic and anorectic neurons of the ARC (as mentioned before) is that peripheral signals of energy can also exert their effects on the LH via the ARC as well as central signals. Also, many other factors in addition to leptin can regulate these neurons, factors like the gut peptide ghrelin which opposes leptin by activating AgRP/NPY neurons (33). When put into perspective in terms of the LH, a hypothesis of how leptin may be inducing its effects can be formed; an increase in leptin would tell the brain that the individual is satiated and needs to reduce their food intake; leptin will act on its receptors in the ARC to reduce NPY/AgRP and increase α-MSH synthesis and release. This would consequently lead to downstream effects on the LH and an alteration in the levels of MCH and ORX (they would be reduced). The converse (for a reduction in leptin) would also be true.

However, data from studies carried out in more recent years suggest that the action of leptin on these leptin receptor (LepRb)-expressing neurons located in the ARC may only be accounting for a small portion of leptin action on energy balance as ARC LepRb neurons together comprise a minority of the total central nervous system LepRb neurons (34). It is unrealistic to believe that the ARC LepRb neurons, a single neural circuit, could be mediating all/the majority of leptin action. Therefore, the LepRb must be expressed in a number of different areas, one of these being the LH. A study by Elmquist et al. examined distributions of mRNA of leptin receptor isoforms in rat brain by using a probe and moderate hybridisation was observed in the LH confirming the presence of the leptin receptor (35). Studies in the last three years have been trying to elucidate some of the neural mechanisms by which leptin may control food reward and investigators have been looking into the interaction of leptin with the mesolimbic dopamine (DA) system which comprises of the ventral tegmental area (VTA) and striatum. The rewarding value of food is largely coded for by the this system and leptin has been found to emit a powerful signal to it (36). It is believed that the LH forms an important part of the mesolimbic reward circuit. As described before, there are two known populations of orexigenic neurons in the LH, one expresses MCH and the other ORX, both of which are inhibited by leptin. These neurons project to the striatum and VTA respectively to alter feeding and measures of reward (37) and has thus lead to the hypothesis that these neurons might contribute to the regulation of the mesolimbic DA system (38). Leinninger et al. explored this hypothesis and found that leptin action via LH LepRb neurons suppresses feeding and that these neurons densely innervate the VTA, confirming that leptin via LH LepRb neurons, modulates the mesolimbic DA reward pathway and decreases feeding.

The experimental evidence discussed strongly demonstrates that the LH plays a large and crucial role in regulating food intake. From initial lesioning experiments carried out in the 1940s to more complex studies involving leptin in recent years; we have learnt that food intake is regulated by complex neuronal circuits and not by specific hypothalamic nuclei as once believed. Studies have shown that the LH communicates with other neuronal systems of food intake, (the NPY/AgRP and POMC/CART neurones of the ARC), peripheral signals like leptin either directly or indirectly (through LepRb ARC neurones) and it also manages to exert an effect on the mesolimbic system associated with reward of food intake. This evidence is proof enough that LH can sense peripheral and central signals of energy, process them and contribute to regulation of food intake. Of course, further research is required to improve our knowledge of what the LH specifically does and to highlight possible targets for intervention to manipulate food intake and therefore body weight but already, piece by piece we have already learnt a great deal about LH’s role in food intake and
will continue to do so in the future.

References
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