I. Obesity & The Brain

Just over 67% of adults in the United States are considered to be overweight or obese. Annually 190 billion dollars is spent on obesity related illness in the United States. Child obesity alone in the U.S. is responsible for over 14 billion dollars in direct medical costs. The biological control of energy balance is a complex system of many organs including the pancreas, the gastrointestinal tract, and the brain. The appeal of food is transmitted by our senses which is then detected by our brain. Additionally, complex hormone and protein pathways create a physiological condition interpreted in the brain that, in turn, regulates appetite.

The hypothalamus is an area of the brain that regulates the endocrine system and pituitary gland based on environmental and internal stimuli to maintain homeostasis. Peptides and hormones interact with the hypothalamus, possibly influencing feeding behavior. A satiety-centered region of interest within the hypothalamus that displays highly significant sensitivity to changes in energy is the Ventromedial Nucleus (VMN). Lesioning of the VMN has been shown to generate hyperphagia in rats (and humans), strongly suggesting a role for the VMN in satiety. Thus, the VMN has become a site of interest in obesity studies.

II. BDNF & Obesity

Brain derived neurotrophic factor (BDNF) is a member of the neurotrophin family highly expressed in the VMN (Fig 3). Neurotrophins are a family of proteins that induce the function, development, and survival of neurons. Given that the VMN has been labeled the “satiation center” it stands to reason that BDNF plays a role in appetite regulation. To test this hypothesis, Wang et al. exogenously injected BDNF into the VMN of mice. Fig 4 below shows that rats injected in the VMN with BDNF reduce their food intake, water intake, and as a result lose weight. Other studies have demonstrated that rodents incapable of producing BDNF develop hyperphagia and obesity. These studies confirm that BDNF plays a significant role in energy homeostasis.

Manipulations of BDNF concentration and synthesis have been shown to change feeding behavior. Under-expression of BDNF leads to hyperphagia while overexpression of BDNF has been linked with anorexia nervosa. Interestingly, BDNF concentrations correlate with many other signals including the hormone leptin, the leptin receptor, the peptide PACAP (pituitary adenylate cyclase activating polypeptide), and the BDNF protein receptor TrkB. These correlations suggest a complex pathway with multiple steps. Stimulation of leptin and PACAP receptors leads to increased BDNF production. Because BDNF is implicated in the onset of hyperphagia and therefore obesity, elucidation of the mechanism that drives this synthesis may result in therapies that could combat obesity.

III. Signaling the Synthesis of BDNF

Evidence from rodent studies suggest that three peptides (leptin, PACAP, and BDNF) acting in the VMN can regulate feeding behavior and body weight. Leptin is synthesized from peripheral adipose cells and transported into the brain whereas PACAP and BDNF are synthesized in the VMN. Administering leptin, PACAP, or BDNF directly into the hypothalamus reduces feeding and body weight. Conversely, pharmacological or genetic blockade of these peptides results in overeating and obesity. However, how these three signals interact with each other in the VMN is still unknown.

Previous hypotheses assumed leptin and PACAP work independently in the VMN to regulate energy homeostasis. However, preliminary data (Fig 7) demonstrate that A) PACAP and BDNF (and leptin receptors) are produced in the same cells in the VMN, B) administering PACAP or leptin in the VMN stimulates BDNF mRNA expression and C) blocking VMN PACAP receptors (PACAP-38) prevents leptin induced feeding suppression9. Thus, our new hypothesis proposes leptin is functionally upstream of PACAP signaling which, in turn, synthesizes BDNF and enables subsequent binding to TrkB receptors resulting in decreased feeding and body weight.

The BDNF gene is located on chromosome 11 and has several alleles. Two alleles of BDNF were studied by Mou et al.9. The two alleles are separated by a T→C intronic SNP. The mutation occurs at the binding site for the transcriptional regulatory protein hnrNDB. The C allele has a much lower binding affinity for hnrNDB and therefore has decreased transcription as seen in the Fig 9 (left). As a result homozgyous CC individuals express much lower concentrations of BDNF in the hypothalamus when compared to CT or TT individuals. The phenotypic result is that CC individuals have greater BMI and body fat percentage, as seen in Fig 10 (right).

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IV. Anatomy of BDNF

BDNF is a 119 amino acid long peptide that may dimerize with itself to create a homodimer or dimerize with other neurotrophins to create a heterodimer. The neurotrophin family displays high sequence homology in seven β-strands that contribute to three antiparallel β sheets that are locked by three disulfide bridges, termed a cysteine knot. Three β-hairpins in loops and a longer loop have higher sequence variability which allows for specificity between the neurotrophins. β-hairpin loop 2 in BDNF binds to its receptor, TrkB.

V. Genetics of BDNF

The mutation from T→C causes BDNF to be under expressed. The high affinity BDNF isoform is associated with the highest BMI and body fat percentage in a cohort of 837 healthy children.

VI. Other Factors Affecting BDNF

Exercise- Physical activity correlates with high concentrations of BDNF. Hippocampal BDNF concentrations increased after exercise in rats. Conversely, rats deprived of exercise exhibited much lower concentrations of BDNF. BDNF concentrations also increased in muscle tissues samples, although the source of BDNF is unknown. Pedersen et al. suggest that the increase of BDNF concentration in muscle tissue is due to locally produced BDNF. It is not well studied if this increase of BDNF is also found in the hypothalamus or if it affects feeding behavior.

VII. Citations


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