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Review

Is obesity a brain disease?

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ABSTRACT

That the brain is involved in the pathogenesis and perpetuation of obesity is broadly self-intuitive, but traditional evaluation of this relationship has focused on psychological and environment-dependent issues, often referred to as the "it's all in the head" axiom. Here we review evidence that excessive nutrition or caloric flux, regardless of its primary trigger, elicits a biological trap which imprints aberrant energy control circuits that tend to worsen with the accumulation of body fat. Structural and functional changes in the brain can be recognized, such as hypothalamic inflammation and gliosis, reduction in brain volume, reduced regional blood flow or diminished hippocampal size. Such induced changes collectively translate into a vicious cycle of deranged metabolic control and cognitive deficits, some of which can be traced back even to childhood or adolescence. Much like other components of the obese state, brain disease is inseparable from obesity itself and requires better recognition to allow future therapeutic targeting.

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1. Introduction

Overeating and sedentary behavior are typically viewed as reflective of cultural, psychological or otherwise acquired addictive traits, abetted by seemingly controllable external cues, the availability of calorie-rich food and the growing ease of life, which now allows lessening linkage between voluntary movement and survival. As such, these behavioral patterns are often the target of moral judgment, which eventually contributes to physician–patient mistrust in the treatment of obesity and its sequels when facing the failure of the "eat less, exercise more" approach. Here we will assess existing evidence that obesity indeed is a disease of the brain. Whether brain disease in obesity is the primary event or at least a partly reversible sequel of obesity may

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matter less than expected from traditional rigid "cause and effect" analysis.

2. Overnutrition is a biological trap, not simply a willful choice

Animal studies may offer good insight into biologically entrenched choices of diet, as they are uncomplicated by cultural and social habituation or the complexity of human cognition. Earlier beliefs that animals can select food with precision sufficient to allow just normal growth and survival have been challenged more than two decades ago (Galef, 1991). Even if such biological precision is accepted, recent data suggest that early exposure of rats to fatty foods during the growth period predisposes these animals to favor high fat diet in adult life (Nakashima and Yokokura, 2010). Long-term, fat- and sugar-rich cafeteria feeding can, in turn, increase energy intake in rats by 25% (Vallerand et al., 1986). It is therefore not surprising that in the setting of multiple choice cafeteria diet in rats, hyperphagia and obesity rapidly evolve (Naim et al., 1985). Further, spontaneously hypertensive rats that were offered a choice between cafeteria diet and regular chow diet not only experienced increased body weight but also featured leptin and insulin resistance and higher blood pressure than control rats fed on regular chow (Miesel et al., 2010). These experiments may have replicated the human metabolic syndrome (MetS) on the genetic background of hypertension. Finally, obesity can be facilitated by ill-programming generated not only by self-feeding, but also by prenatal and postnatal maternal exposure, as the feeding of rats with cafeteria diet during gestation and lactation results in offspring adiposity (Bayol et al., 2005, 2008). Such adipose accumulation is already complicated by the presence of non-alcoholic fatty liver, independent of actual diet of the pups themselves (Bayol et al., 2010; Hennige et al., 2009).

Both the caloric source and time of eating may be as important as the high caloric value of the consumed food. In one study, mice fed a diet supplemented with monounsaturated fatty acids displayed more efficient insulin action in the brain and enhanced brain cortical activity and locomotion than mice receiving a calorically equal food containing saturated fatty acids only (Sartorius et al., 2012). Restricting high fat diet to several hours a day leads to lesser weight gain than a calorically equivalent diet given with continued free access to food (Sherman et al., 2012). Conversely, there is evidence that "out of phase" consumption of food (during hours which are normally spent in the inactive, food-free state, typical of the undisturbed circadian rhythm) can facilitate weight gain without an overall increase in caloric intake (Salgado-Delgado et al., 2010).

3. Early life overnutrition and exposure to maternal obesity reprograms eating control in adult life

Brain structural maturation is not completed in-utero but extends into the first phases of life. Hence, exposure to excessive nutrition during this critically vulnerable pre- and postnatal development periods can impair the brain in general and disrupt the finely tuned normal brain-governed feeding behavior. Such responses to over-nutrition are probably mediated through the induction of structural and functional alterations which can lead to obesity, dysmetabolism and/or cognitive disadvantage later in life. For example, in one study high fat diet resulted in increased body fatness when administered either in weaning or adult mice, but only juvenile exposure to fatty food reduced hippocampal neurogenesis and relational memory flexibility (Boitard et al., 2012). Maternal high fat diet maintained from pre-mating through lactation led to increased offspring hippocampal lipid peroxidation and decreased neuogenesis (Tozuka et al., 2009). Newborn rat pups raised on a high-carbohydrate (HC) milk formula develop chronic peripheral hyperinsulinemia and adult-onset obesity despite subsequent placement on regular rat chow. This is associated with impaired hypothalamic energy control manifested by increases in the mRNA expression of hypothalamic orexigenic hormones such as neuropeptide Y (NPY), agouti-related polypeptide, and galanin and decreased the mRNA expression of feeding down regulators including proopiomelanocortin (POMC), melanocortin receptor-4, cocaine- and amphetamine-regulated transcript, and corticotrophin-releasing factor which persisted at least into young adulthood (Srinivasan et al., 2008).

Although caloric restriction can later reduce body weight gain, the earlier life-entrained hypothalamic predisposition to hyperphagia appears irreversible (Srinivasan et al., 2013). Apparently, early life exposure to unnecessarily enriched nutrition imprints hypothalamic feeding related aberrations that may be *macronutrient-dependent* rather than *calorie-related*: for example, as compared to maternal high-fat diet, high carbohydrate diet resulted in lower arcuate nucleus POMC expression (which encodes at this site the appetite curbing hormone α melanocyte-stimulating-hormone, α MSH) and higher paraventricular nucleus NPY and orexin peptide concentrations in their young adult rat offspring (Beck et al., 2012). Not only direct nutritional effects are important but also maternal obesity status per se may be a dominant factor: cross-fostering of offspring of lean rat dams by obese dams resulted in an exaggerated dysmetabolic, insulin-resistant phenotype compared to offspring lean dams nursed by their natural mothers (Oben et al., 2010). In humans, where calorie-rich diet is normally excessive in terms of both fat and carbohydrates, a mixed deleterious hypothalamic derangement may therefore evolve.

This complex pattern may be, however, further modulated by intestinal signals generated by colonic microbiota. Dietary fibers such as inulin-type fructans, which are non-digestible by human enzymes but are easily fermented by gut bacteria can modify the gut microbioata profile in association with increases in circulating gut hormones which tend to curb appetite such as Glucagon-Like-Peptide 1 (GLP-1), peptide YY and decrease of the gastric-derived orexigenic hormone ghrelin (Cani et al., 2005; So et al., 2007). Accordingly, in mice, supplementation of a high fat diet with oligofructose-enriched inulin was shown to reduce accrued fat deposition and increase arcuate nucleus neuronal activity as captured by manganese-enhanced MRI (Anastasovska et al., 2012).

4. Overnutrition elicits brain disease: relation to obesity

Cafeteria diet reportedly disrupts the blood brain barrier in the hippocampus in rats through down regulation of mRNA expression of tight junction proteins, particularly Claudin-5 and -12, in the choroid plexus (Kanoski et al., 2010), thus exposing the brain tissue to potentially damaging circulating factors which cannot normally interact with brain cells. Chronic high fat intake can lead to inflammatory changes in the brain cortex as evidenced by the presence of increased nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-generated reactive oxygen species and accelerated prostaglandin E2 production along with up-regulation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling in mice fed a fat-rich diet leading to obesity (Zhang et al., 2005). This indicates that brain oxidative stress could potentially mediate the pathogenesis of overnutrition-related metabolic diseases. Obesity related inflammatory changes within the brain have selective sequels affecting energy homeostasis and general functional and structural implications. For example, obesity linked to mitochondrial dysfunction in hypothalamic POMC neurons can cause impairment in central glucose sensing (Parton et al., 2007).

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