Understanding the mechanisms of food intake and obesity

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Background

Rapid progress is being made in understanding the brain-processing and related psychology of the sensory properties of food, and how the satiety (fullness) signals produced during and after eating regulate appetite. While brain mechanisms control appetite, a number of sensory and environmental factors contribute to overstimulation of the sensory systems, producing sensory reward signals that are stronger than can always be controlled easily by satiety signals (1,2).

This knowledge makes it seem very likely that, while satiety signals have not changed in the last 30 years, changes in the same period in the sensory side of the control process mean that they are now being overridden, contributing to the increasing incidence of obesity. One implication of this work is that, if factors on the sensory side of the appetite control process could be regulated, it would open avenues to address obesity prevention and control.

From the neuroscience and psychology perspective, there are, however, many other mechanisms that interact with the brain and contribute to obesity.

Genetic factors

These are of some importance, with, for example, the heritability of body mass index estimated from twin studies being in the region of 0.66–0.70 (3–6). However, the 'obesity epidemic' that has occurred since 1990 cannot be attributed to genetic changes, for which the timescale is far too short, but instead to factors such as the increased palatability, variety and availability of food (as well as less exercise), which are some of the crucial drivers of food intake and the amount of food that is eaten (1,2,7,8). Of course, understanding genetic factors may lead to treatments for some cases of obesity, and to better understanding of individual differences that help to account for why some people become obese in our changed environment (see contribution by Farooqi and O'Rahilly, p. 37 (6)).

Endocrine factors and their interaction with brain systems

There are many hormones that are released when food is eaten, and some of these are important in regulating appetite, including leptin. However, cases of obesity that can be related to changes in the leptin hormone satiety system are very rare (6,9). Further, obese people generally have high levels of leptin, so leptin production is not the problem. Instead, leptin resistance (i.e. insensitivity) may be somewhat related to obesity, with the resistance perhaps related in part to smaller effects of leptin on hypothalamic arcuate nucleus NPY/AGRP neurones (10). Indeed, rapid advances are being made in understanding how hormones such as leptin influence peptide brain systems in the hypothalamus that are important in the control of food intake (4,5,11). However, at least at present only a small proportion of

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cases of obesity can be related to gene-related dysfunctions of the peptide systems in the hypothalamus, with, for example, 4% of obese people having deficient (MC4) receptors for melanocyte-stimulating hormone (4,5,11).

It is unlikely that changes in these hormonal systems in the last 30 years are the cause of the increasing incidence of obesity, although understanding these endocrine systems that produce satiety and hunger signals may be useful in the treatment of some cases of obesity (see contribution by Bloom, p. 63).

Brain processing of the sensory properties and pleasantness of food

A conceptual diagram to show how the sensory signals produced by food interact in the brain with satiety signals in order to produce an output that represents the reward, hedonic or appetitive value of the food, and which leads to eating, is shown in Fig. 1.

When the satiety signals produced, for example, by gastric distension and gut hormones are minimal, the sensory properties of food become rewarding and pleasant, appetite for the food is present, and eating is likely to occur. After a meal, when satiety signals are present, the sensory properties of food are no longer interpreted as pleasant, and there is no appetite for the food. The site of the interaction between satiety signals and sensory signals including the taste, smell, texture and sight of food to produce a hedonic or affective evaluation of the food occurs in brain regions such as the hypothalamus shown in Fig. 2. The hypothalamus contains neurones with different peptide transmitters that are sensitive to some of the hormonal and neural signals from the body that influence hunger vs. satiety, including leptin (4,5,11). The hypothalamus also contains neurones that respond to the sight, taste and smell of food, but only if hunger is present (1,2,7,8).

However, the hypothalamus is not the first stage of brain processing at which this interaction between the sensory inputs produced by the sight, smell, taste and texture of food and hunger/satiety signals occurs, for all these sensory signals are represented in the orbitofrontal cortex (see Fig. 2), and the neurones here only respond to food if hunger is present (1,2,7,8). The orbitofrontal cortex is a crucial region for this interaction, for neurones at earlier stages of sensory processing, for example, in the primary taste cortex and the inferior temporal visual cortex, respond to taste and visual inputs independently of whether hunger is present (1,2,7,8). These earlier stages of processing thus represent what sensory stimuli are present, but not how pleasant they are. Therefore, the orbitofrontal cortex is a crucial site for the interaction between sensory inputs produced by food and hunger/satiety signals, because this system determines how pleasant a food is and whether we have an appetite for it. It is likely that the hypothalamic neurones that respond to hunger/satiety signals send connections to the orbitofrontal cortex to inform it of these signals. It is also likely that the source of the inputs to the hypothalamus that result in hypothalamic neurones only responding to the sensory properties of food if hunger is present is the orbitofrontal cortex (see Fig. 2) (1,2,7,8).

Studies on orbitofrontal cortex neurones are already revealing, for example, how the texture of fat is represented in the mouth (which has implications for the development of palatable low-fat foods); and the mechanisms of sensory-

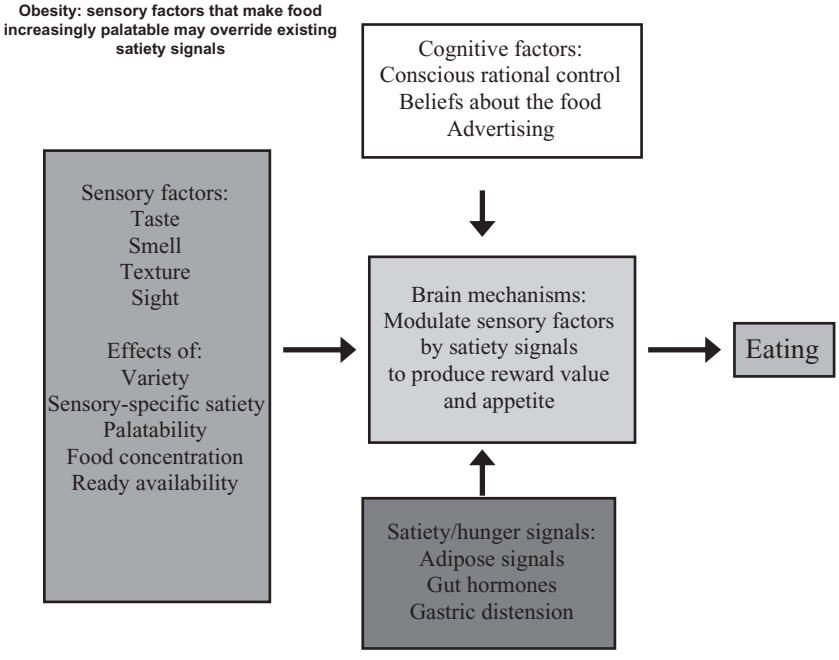

Figure 1 Schematic diagram to show how sensory factors interact in the brain with satiety signals to produce the hedonic, rewarding value of food, which leads to appetite and eating. Cognitive factors directly modulate this system in the brain.

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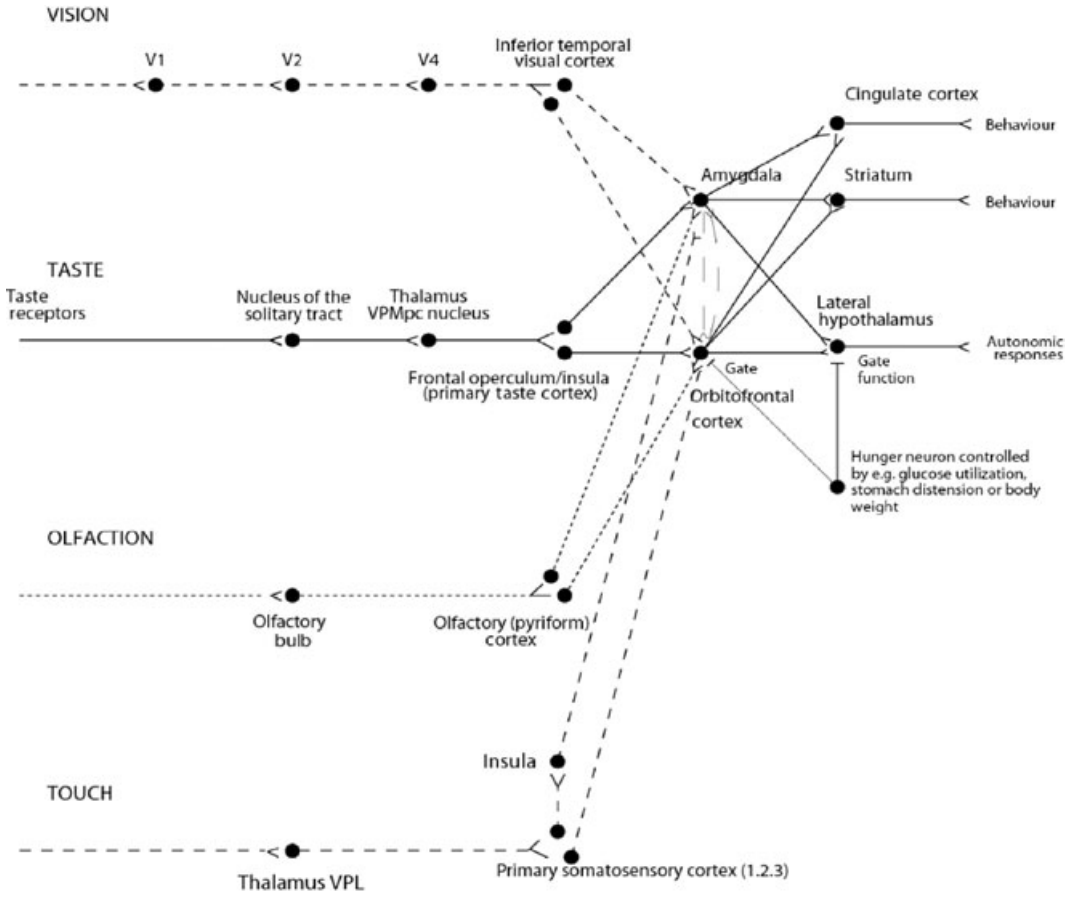

Figure 2 Schematic diagram of the taste and olfactory pathways in primates, including humans, showing how they converge with each other and with visual pathways. Hunger modulates the responsiveness of the representations in the orbitofrontal cortex of the taste, smell, texture and sight of food (indicated by the gate function), and the orbitofrontal cortex is where the palatability and pleasantness of food is represented. VPL, ventralposterolateral; VPMpc, ventralposteromedial thalamic nucleus; V1, V2, V4, visual cortical areas.

specific satiety (the decrease in appetite for one food when eating it, while not affecting the appetite for other foods) and of incentive motivation (the increase in appetite that occurs early on in a meal when food is first made available), which are important factors in how much food is eaten in a meal (1,7,8,12).

Many of these investigations have been performed by neuronal recording in macaques because the taste and visual pathways are quite similar in macaques and humans, and because the crucial information that is being represented can be studied in detail in this way. These studies have led to complementary functional neuroimaging studies in humans, which are confirming that these concepts apply to humans. For example, the human orbitofrontal cortex has large activations when food is smelled (13), or when it is in the mouth (14). This is only if hunger is present. Sensory-specific satiety is represented in the human orbitofrontal cortex but not at earlier stages of processing (14). Moreover, the texture of food in the mouth, including the texture of fat, which contributes to making some foods palatable, is represented in the orbitofrontal cortex and an area to which it connects, the anterior cingulate cortex (15). It is of importance for future studies to determine how these brain systems may respond differently in different individuals in order to help us understand which brain systems may respond differently in, for example, obesity. A recent study of individual differences found that the orbitofrontal cortex, the cingulate cortex, and the ventral striatum respond more to the sight and flavour of chocolate in chocolate cravers compared with chocolate non-cravers (16).

The concept for the brain organization of the control of appetite is thus that convergence of sensory inputs produced by the taste, smell, texture and sight of food occurs in the orbitofrontal cortex to build a representation of food flavour. The orbitofrontal cortex is where the pleasantness and palatability of food are represented, as shown by the discoveries that these representations of food are only activated if hunger is present, and correlate with the subjective pleasantness of the food flavour (1,7,8). The orbitofrontal

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cortex representation of whether food is pleasant (given any satiety signals present) then drives brain areas, such as the striatum and the cingulate cortex, which in turn lead to eating behaviour (see Figs 1 and 2).

This concept is fundamental to understanding the rise in obesity. During the last 30 years, sensory stimulation produced by the taste, smell, texture and appearance of food, as well as its availability, has increased dramatically, yet the satiety signals produced by stomach distension, satiety hormones, etc. have remained essentially unchanged, so that the effect on the brain's control system for appetite (as shown in Figs 1 and 2) is to lead to a net average increase in the reward value and palatability of food, which overrides the satiety signals and contributes to the tendency to be overstimulated by food and to eat too much of it.

In this scenario, it is important to better understand the rules used by the brain to produce the representation of the pleasantness of food and how the system is modulated by eating and satiety. This understanding, and how the sensory factors can be designed and controlled so as not to override satiety signals, are important research areas in the understanding, prevention and treatment of obesity. Advances in understanding the receptors that encode the taste and olfactory properties of food (17) and the processing in the brain of these properties (1,7,12) are also important in providing the potential to produce highly palatable food that is at the same time nutritious and healthy.

The brain has thus been built to use certain rules to determine how pleasant a food is at a particular time, and therefore whether a food should be eaten. Psychological studies have revealed some of the rules of operation of these brain systems that determine the pleasantness of food, and also how many of the relevant factors could in combination produce a tendency to over-eat. These factors may be important in driving the current obesity epidemic and their control should be one approach to the prevention and treatment of obesity.

Food palatability

A factor in obesity is food palatability, which, with modern methods of food production, can now be greater than would have been the case during the evolution of our feeding control systems. These brain systems evolved so that internal signals from, for example, gastric distension and glucose utilization could act to decrease the pleasantness of the sensory sensations produced by feeding sufficiently by the end of a meal to stop further eating (1,2,7,12). However, the greater palatability of modern food may mean that this balance is altered. This 'extra' palatability means that it is insufficiently decreased after a standard amount of food has been eaten, leading to extra food being eaten (see Fig. 1).

Sensory-specific satiety, and the effects of variety on food intake

Sensory-specific satiety is the decrease in the appetite for a particular food as it is eaten in a meal, without a decrease in the appetite for different foods (1,2,7,12). It is an important factor influencing how much of each food is eaten in a meal, and its evolutionary significance may be to encourage the eating of different foods, thus obtaining a range of nutrients. As a result of sensory-specific satiety, if a wide variety of foods is available, over-eating in a meal, and in the longer term, can occur (18). Given that it is now possible to make available a very wide range of food flavours, textures and appearances, and that such foods are readily available, this variety effect may be a factor in promoting excess food intake and obesity (19).

Fixed meal times and the availability of food

Another factor that could contribute to obesity is fixed meal times. The normal control of food intake by alterations in inter-meal interval is not readily available in humans, and food may be eaten at a mealtime even if hunger is not present (1). Even more than this, because of the high and easy availability of food (in the home and workplace) and stimulation by advertising, there is a tendency to start eating again when satiety signals after a previous meal have decreased only a little ('grazing'), and the consequence is that the system again becomes overloaded.

Food saliency and portion size

Making food salient (prominent), for example, by placing it on display, may increase food selection, perhaps particularly in the obese (20–23). Portion size is also a factor, with more being eaten if a large portion of food is presented (24). Whether this is a factor that can lead to obesity and not just altered meal size is not yet clear. The driving effects of visual and other stimuli, including the effects of advertising, on the brain systems that are activated by food reward may be different in different individuals, and may contribute to obesity (see contribution by Wardle, p. 73).

Energy density of food

Although gastric emptying rate is slower for foods of high energy density, this does not fully compensate for the energy density of the food (25,26). The implication is that eating energy-dense foods (e.g. high-fat foods) may not allow gastric distension to contribute sufficiently to satiety (see contribution by Jebb, p. 93). Because of this, the energy density of foods may be an important factor that influences how much energy is consumed not only in a meal, but also

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in the longer term (27), and there are differences between individuals in whether they become obese on a high-fat diet (28). Indeed, it is notable that obese people tend to eat foods with high energy density, and to visit restaurants with energy-dense (e.g. high-fat) foods. It is also a matter of clinical experience that gastric emptying is faster in obese than in thin individuals, so that gastric distension may play a less effective role in contributing to satiety in the obese.

Eating rate

Eating rate, which is typically fast in the obese (29), may provide insufficient time for the full effect of satiety signals as food reaches the intestine to operate.

Stress

Another potential factor in obesity is stress, which can induce eating and could contribute to a tendency to obesity (see contribution by Wardle, p. 73). In a rat model of this, mild stress in the presence of food can lead to over-eating and obesity. This over-eating is reduced by anti-anxiety drugs.

Binge-eating

Binge-eating has some parallels to addiction. In one rodent model of binge-eating, access to sucrose for several hours each day can lead to binge-like consumption of the sucrose over a period of days (30–33). Binge-eating is associated with the release of dopamine. Binge-eating is brought close to an addictive process, at least in this model, in that after the binge-eating has become a habit, sucrose withdrawal decreases dopamine release in the ventral striatum (a part of the brain involved in addiction to drugs such as amphetamine). Altered binding of dopamine to its receptors in the ventral striatum is produced, and signs of withdrawal from an addiction occur, including teeth chattering. In withdrawal, the animals are also hypersensitive to the effects of amphetamine. Another rat model examines binge-eating of fat, and is being used to investigate whether the reinforcing cues associated with this can be reduced by the GABA-B receptor agonist baclofen (34).

Energy output and exercise

If energy intake is greater than energy output, body weight increases. Energy output is thus an important factor in the equation. A lack of exercise, or the presence of high room temperatures, may tend to limit energy output, and thus contribute to obesity. It should be noted, though, that obese people do not generally suffer from a very low metabolic rate: in fact, as a population, in line with their elevated body weight, obese people have higher metabolic rates than normal-weight humans (35). It has been shown that exercise can make some contribution to reducing body weight (36).

Cognitive factors

It has been shown that cognitive factors, such as preconceptions about the nature of a particular food or food odour, can reach down into the olfactory system in the orbitofrontal cortex, which controls the palatability of food, to influence how pleasant an olfactory stimulus is (37). This has implications for further ways in which food intake can be controlled, and needs further investigation.

The psychology of compliance with information about risk factors for obesity

It is important to develop better ways to provide information that will be effective in the long term in decreasing food intake while maintaining a healthy diet, and in promoting an increase in energy expenditure, for example, by encouraging exercise. Although modest success can be achieved by behavioural treatments that focus on helping people to control exposure to cues that trigger eating (see contribution by Wardle, p. 73), it is suggested that it will be important to take into account in treatment programmes as many as possible of the factors reviewed here, as it is these factors that are important contributory factors to the current obesity epidemic.

Conclusion

Rapid advances are being made in neuroscience and psychology in identifying and understanding some of the many factors that influence food intake and energy output, and thus obesity. It is crucial to develop this understanding further, as there is great potential to use this knowledge in the prevention and treatment of obesity. Many of the factors described need to be understood much better, but, in addition, it is important to develop ways to prevent and treat obesity that combine changes in many of the factors described above. For this reason, we need to understand how they interact and how humans can be helped to control their body weight using the most effective combinations of these, as well as perhaps other as yet unknown, factors.

Factors that contribute to driving people towards obesity include the greater stimulation in the last 30 years of the brain by sensory stimuli that make food palatable and pleasant, relative to internal satiety signals, which have remained unchanged in this short time. In this situation, it is important to understand the rules used by the brain to produce the representation of the pleasantness of food much better, and how the system is modulated by eating and satiety.

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The factors that contribute to overstimulating the brain's food reward systems relative to satiety signals include food palatability and appearance, sensory-specific satiety, food variety, food availability, the effects of visual stimulation and advertising, the energy density and nutritional content of food, portion size, and cognitive states. We will need to provide clear information about these and other factors including risks to the public, and to emphasize that it may be necessary to pay attention to all of them in order to control body weight.

Conflict of Interest Statement

No conflict of interest was declared.

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