



# The role of dopamine in the pursuit of nutritional value



James Edgar McCutcheon

Dept. of Cell Physiology and Pharmacology, Maurice Shock Medical Sciences Building, University of Leicester, University Road, Leicester LE1 9HN, United Kingdom

## HIGHLIGHTS

- Procurement of foods high in nutritional value is critical for all organisms.
- Post-ingestive processes signal reinforcement value by evoking dopamine.
- Dopamine is especially important for linking food cues to post-ingestive reward.
- These processes have implications for human health and obesity.

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## ABSTRACT

Acquiring enough food to meet energy expenditure is fundamental for all organisms. Thus, mechanisms have evolved to allow foods with high nutritional value to be readily detected, consumed, and remembered. Although taste is often involved in these processes, there is a wealth of evidence supporting the existence of taste-independent nutrient sensing. In particular, post-ingestive mechanisms arising from the arrival of nutrients in the gut are able to drive food intake and behavioural conditioning. The physiological mechanisms underlying these effects are complex but are believed to converge on mesolimbic dopamine signalling to translate post-ingestive sensing of nutrients into reward and reinforcement value. Discerning the role of nutrition is often difficult because food stimulates sensory systems and post-ingestive pathways in concert. In this mini-review, I discuss the various methods that may be used to study post-ingestive processes in isolation including sham-feeding, non-nutritive sweeteners, post-ingestive infusions, and pharmacological and genetic methods. Using this structure, I present the evidence that dopamine is sensitive to nutritional value of certain foods and examine how this affects learning about food, the role of taste, and the implications for human obesity.

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## 1. Introduction

In the 1930s Curt Richter outlined the importance of behaviour as a means for animals to regulate physiological state in a homeostatic manner [1]. One focus of his research was the ability of rats to guide their behaviour towards certain nutrients in times of deficit. Potentially, the most fundamental form of such behavioural homeostasis is an organism's drive to acquire enough food to supply its energetic needs. Accordingly, a number of mechanisms have evolved to allow animals to accomplish this including sensory systems, such as taste, as well as the ability to detect nutrients post-ingestively.

Identifying the precise mechanisms that underlie the ability to detect nutritional value is challenging, particularly their neurobiological basis, because several distinct processes normally occur in concert. For example, ingestion of sugar stimulates taste receptors in the oral cavity as well as providing post-ingestive feedback via peripheral actions

including activation of receptors and/or transporters, release of hormones such as insulin, and cellular glucose oxidation. Thus, the vast majority of experiments examining the neurobiology of feeding behaviour cannot separate the contribution of taste from that of post-ingestive effects. However, a number of methods have been developed that allow these processes to be studied independently of one another (see Section 3).

The neurotransmitter dopamine has long been associated with feeding behaviour, motivation, reward and reinforcement, and associative learning [2,3], all of which could be presumed important in the procurement of nutritional value. In this review, I will discuss the evidence that the dopamine system is exquisitely sensitive to certain nutrients and argue that this is an essential way in which an organism can activate behavioural plans that maintain nutrient homeostasis. I will present research using different methods of either isolating or eliminating the role of nutritional information and describe how these impact the dopamine system. In addition, the mechanisms by which this information is relayed to the brain will be examined including the possibility that different nutrients are signalled through different pathways. The role that

E-mail address: [jem64@le.ac.uk](mailto:jem64@le.ac.uk).

food-associated cues play in driving feeding behaviour and the sensitivity of these cues to the post-ingestive consequences of the nutrients that they predict will be examined. Finally, the implications of this research for feeding behaviour in humans and obesity will be discussed.

**2. An essential role for dopamine in feeding**

The involvement of dopamine in feeding behaviour has been recognised for several decades. A dramatic demonstration of this necessity is shown in mice that are genetically engineered to lack dopamine by mutation of tyrosine hydroxylase (dopamine-deficient mice or DD mice) [4]. These mice starve to death unless supplied with an alternative source of dopamine either via administration of the dopamine precursor, L-DOPA, or viral expression of functional enzyme [5]. What these experiments make clear is that although dopamine is essential for feeding, its precise role remains uncertain. For example, motivation to feed seems to be affected in DD mice rather than preference for rewarding foods and palatability [6]. Moreover, dopamine has been implicated in multiple aspects of feeding behaviour including sensory components, learning, relaying physiological state, providing motivation, and finally, encoding nutrient content. Importantly, however, the participation of dopamine in feeding seems to be highly conserved and has been shown in a wide range of species including *Drosophila* [7], rats [8], mice [4], non-human primates [9], and humans [10].

Convincing demonstrations of the role of dopamine in modulating specific aspects of feeding have been obtained using methods that allow activity of the dopamine system to be measured in real-time during feeding behaviour. As such, electrophysiological recordings of dopamine neuron activity or measurement of dopamine concentration in terminal fields with either microdialysis or fast-scan cyclic voltammetry have shown that the presentation of food stimuli reliably evokes neuronal activity and dopamine release across the striatum [11–14]. Such responses have been observed to a wide range of different food stimuli and under different experimental conditions. The magnitude and probability of occurrence of such signals can be modulated by properties of the food such as its novelty, and the physiological state of the subject [3,11,15,16]. In this review, my focus will be one specific question: how relevant is the nutritional content of a food stimulus for the dopamine activity evoked by food or food-associated stimuli?

**3. Methods for isolating the contribution of nutritional content**

A major challenge in studying the neurobiology underlying post-ingestive signalling is that ingestion of food engages multiple sensory components and elicits post-ingestive effects. Therefore, most studies examining the neurobiology of feeding inherently confound contributions from several sensory modalities (e.g. taste, smell,

somatosensation) and post-ingestive processes, including nutrient-sensing. Thus, specific experimental manipulations have been devised in an attempt to study each process in isolation (Fig. 1).

One such method, which has been used to remove post-ingestive processes from the study of feeding behaviour, is the sham feeding paradigm (Fig. 1A) [17]. Here, animals are typically implanted with a gastric fistula, which allows them to feed while any substance consumed leaves the stomach before being absorbed or processed. Thus, the effect of orosensory stimulation in the absence of post-ingestive effects can be determined.

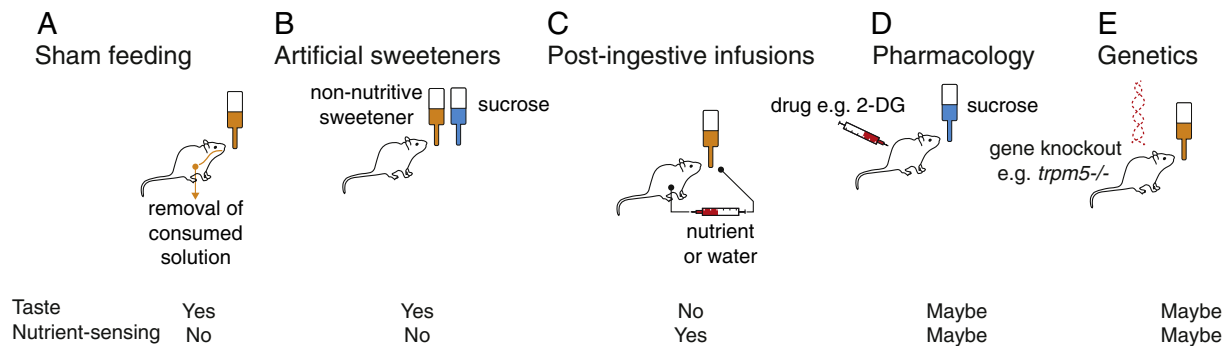
Another method of isolating post-ingestive processes is to use non-nutritive artificial sweeteners (Fig. 1B). Examples are acesulfame K, saccharin, and sucralose. The sweetness of these products can, in theory, be matched to real sugars, such as sucrose or glucose, and responses to each can be compared. However, care must be taken with these studies as precisely matching the orosensory component is challenging, if not impossible. Additionally, preference for each sweetener varies across species and individuals such that matching the taste or flavour of a real sugar to a non-nutritive sweetener might not be possible [18,19].

Direct infusions of nutrients into various compartments of the gastrointestinal (GI) tract or vasculature can be used to probe the post-ingestive effects of nutrients in isolation from other components of feeding behaviour (Fig. 1C). Such infusions may be made in the absence of any behaviour or be triggered by an operant response. These techniques have formed the basis for a pioneering collection of flavour-nutrient conditioning studies by Sclafani and colleagues, which have provided a great deal of fundamental knowledge regarding how post-ingestive effects interact with behaviour [20]. Moreover, infusions into different sites may be used to probe the exact mechanisms by which nutrients are signalled to the brain.

Pharmacological manipulations may provide insight into whether a specific biological mechanism relating to nutrient signalling is involved in feeding (Fig. 1D). For example, the use of the nonmetabolizable glucose analogue, 2-deoxyglucose (2-DG), has been used to demonstrate a role for glucose utilization in several processes [21].

Finally, genetic methods may be used to remove a certain component of feeding behaviour (Fig. 1E). One example is that knockout of the transient receptor potential channel M5 (TRPM5), which is essential for the transduction of sweet taste (and bitter and umami), has been used to generate mice that are ‘sweet-blind’. This mutant line has allowed study of the post-ingestive effects of ingested sugars in isolation from taste-mediated effects [22].

It should be noted that these methods do not need to be used in isolation and, in fact, often are combined. For example, in flavour-nutrient conditioning paradigms, post-ingestive infusions are regularly used in combination with artificial sweeteners so that sweet-tasting food stimuli can be combined with varying degrees of nutrient provision.



**Fig. 1.** The role of nutritional content in driving behaviour can be studied by isolating it from taste or by removing its influence. (A) In sham feeding experiments a gastric fistula allows ingested solution to be removed from the stomach so that there is minimal absorption by the GI tract. (B) Artificial sweeteners provide stimulation of taste pathways without producing post-ingestive consequences. (C) Post-ingestive infusions of nutrients can be made into the GI tract or vasculature to study nutrient sensing in the absence of taste input. (D) Pharmacological agents may be used to disrupt either post-ingestive or taste processes. (E) Genetic methods can be used to alter signalling in pathways necessary for either taste or nutrient sensing.

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