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Review

Circuit organization of sugar reinforcement

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HIGHLIGHTS

- High-potency artificial sweeteners and glucose-containing sugars produce divergent responses in the brain's reward circuitry.
- Separate populations of dopaminergic neurons encode the gustatory and nutritive values of sugar in both rodents and flies.
- This arrangement allows animals to prioritize energy seeking over taste quality.
- Specialized subpopulations of dopamine-containing neurons may form a class of evolutionary conserved chemo- and nutrient-sensors.

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ABSTRACT

Sugar's potent reinforcing properties arise from the complex interplay between gustatory and nutritive signals. This commentary addresses a unique organizational aspect of the neuronal circuitry that mediates sugar reinforcement in both *Drosophila* and rodents. Specifically, current evidence supports a general circuit model where separate populations of dopaminergic neurons encode the gustatory and nutritive values of sugar. This arrangement allows animals to prioritize energy seeking over taste quality, and implies that specialized subpopulations of dopamine-containing neurons form a class of evolutionary conserved chemo- and nutrient-sensors.

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1. Sugar, sweetness, and reinforcement

From its inconspicuous origins during the rise of agriculture, to our modern food environment, refined sugar has made a remarkable journey only to become our main dietary source of excess calories [1,2]. Sheer physiology accounts for this seemingly unlimited appetite for glucose-containing sugars. First of all, D-glucose was selected by most species to be the preferred fuel for brain cells [3]. Therefore, the motivation to maintain high levels of circulating glucose is obviously high for any organism carrying a glucose-dependent brain. Compounding to this critical neurological function, the relatively low levels of stored glucose in our bodies – much lower than for lipids – impose the need for

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continuous sugar procurement and, if available, consumption [according to one estimate, an actively exercising adult human is expected to run out of glycogen stores within 100 min, 4]. In sum, a brain hungry for glucose, encased in a body limited in glycogen, must be equipped with a reward system that is highly sensitive to sugar molecules.

Nature did in fact design an ingenious tactic to innately drive organisms towards sweet sugars such as glucose: specialized sugar receptors lie on the oral epithelium, in such a way that a neural "labeled line" directly connects their activation to brain centers promoting ingestive behaviors [5]. More specifically, it has been determined that taste cell identity is the critical factor determining the type of behavioral response that ensues receptor activation. For example, one can provoke aversive taste reactions to a sweet solution by inducing expression of the sweet receptor gene in cells normally expressing bitter receptors [6]. In other words, activating a certain subpopulation of taste cells results in a prespecified behavioral response, implying that the particular wiring of the connection between taste cells to the brain is the ultimate controller of ingestive programs.

However, sugars impact on the nervous system not only via activation of gustatory cells. The so-called "post-ingestive" signals not only act to limit intake, but also to induce preference formation for energy-containing substances like glucose. In a series of seminal studies in the 1960's, G. Holman demonstrated that systematically pairing an arbitrary flavorant to intra-gastric infusions of glucose would eventually bias preferences towards that same flavorant ["flavor-nutrient conditioning", 7]. Moreover, further studies by A. Sclafani and colleagues demonstrated that intra-gastric infusions of sugar would also strongly enhance the overall intake levels of the associated sweetened flavorant ["appetition", 8].

But the unconditioned post-ingestive signal drives intake not only via Pavlovian associations with sweetened flavorants; specifically, these physiological signals can act independently of gustatory activation to promote food seeking. In other words, the reward value of nutrients like glucose is separately encoded in neural circuits, independently of associations with taste. Thus, sweet-blind mice can efficiently learn to appreciate the nutritional value of sugar, but not artificial sweeteners, by associating nutritional content with spatial locations rather than with taste [9]. Consistently, sugar was also found to activate the reward-related neurotransmitter system of sweet-blind mice [9]. Most likely as a consequence of the existence of a separate sensory channel for post-ingestive factors, mice were also found to prefer aversive bitter tastants that had been paired with intra-gastric glucose infusions over artificial sweeteners paired to intra-gastric infusions of the same sweetener [10]. Thus, sweetness appears to function primarily as a sensory cue that drives animals towards energy sources – rather than acting as a behavioral goal in and by itself. So how do the brains of glucose-starving organisms solve the decision-making problem of prioritizing energy seeking over taste quality? The answer lies in the wiring diagram of sugar-sensitive neural circuits.

2. Separate dopaminergic pathways encode gustatory and nutritional values of sugar

2.1. Rodents

It is therefore to be expected that sugar would activate the primitive, evolutionary old brain circuits that mediate reinforcement learning. In the brain of vertebrates, the striatal areas of the basal ganglia are critical for selecting reward-based actions and evaluating their outcome [11–13]. Within the striatum, the anatomical segregation between dorsal and ventral sectors, each defining their respective efferent targets, is an evolutionarily conserved trait [14]. These two separate striatal sectors have been previously linked to a number of dissociable behavioral reward functions [12,15]. Critically, the catecholamine dopamine, synthetized in ventral mesencephalic nuclei, acts as the major controller of striatal function upon its release from terminal fibers arising from midbrain [13,16,17]. Two particular clusters of midbrain dopamine cells, the ventral tegmental area and the *Substantia Nigra pars compacta*, preferentially terminate within the ventral and dorsal regions of striatum, respectively; this pattern defines, in turn, the mesolimbic (ventral) and nigrostriatal (dorsal) dopaminergic pathways [18].

Within the context of sugar reward, a logical question is whether the dissociation between gustatory (sweet) vs. post-ingestive rewards reflects this anatomical specialization within ventral and dorsal dopaminergic-striatal pathways. A recent study from our group explicitly tested this hypothesis [10]. Dopamine release was monitored in both ventral ("VS") and dorsal ("DS") striatal sectors during the active intake of either nutritive or non-nutritive sweeteners. This was achieved by collecting fluid samples from striatum using microdialysis probes, followed by chromatographic-electrochemical determination of dopamine moieties [e.g. 19]. To overcome potential issues associated with differences in gustatory quality between sugars and sweeteners, the following procedure was adopted. Mice licked a spout containing a non-caloric sweetener (i.e. sucralose), such that triggering a contact-based lick counter prompted intra-gastric infusions of solutions containing either sucralose or glucose (i.e. its metabolic usable enantiomer D-glucose).

Tellez et al. [10] observed robust rises in extracellular dopamine levels in VS during sweetener intake, irrespective of which solution was being administered to the gut – a result that points to a preponderant role for gustatory (sweet) signals in the control of dopamine release in VS. Interestingly, however, dopamine release in DS increased above baseline levels only when sweetener intake was accompanied by intra-gastric infusions of D-glucose – thereby suggesting a selective sugar-sensing role for DS-projecting dopamine cells.

Gustatory vs. nutritional sensing capabilities in VS vs. DS was more clearly demonstrated by an experiment in which the sweet sucralose solution was adulterated by adding the aversive bitter compound denatonium benzoate, but in such a way that licking this sweet/bitter stimulus still resulted in intra-gastric D-glucose. Ingesting the sweet/bitter stimulus suppressed (intra-gastric) sugar-induced dopamine release in VS; however, and rather remarkably, evoked dopamine release rose above baseline levels in DS — such that sugar-induced dopamine release in DS remained equally robust notwithstanding the extreme differences in taste quality. In sum, while sugar drives dopamine efflux in VS when administered directly into the gut [19], such phenomenon is under tight control of the gustatory system.

But is the reciprocal true? That is, would a non-metabolizable glucose analogue fail to enhance dopamine efflux in DS? This was demonstrated by an experiment in which licking the sweet sucralose stimulus resulted in intra-gastric infusions of the non-metabolizable enantiomer L-glucose [10]. While this procedure completely suppressed sugar-induced dopamine release in DS, sweetness-induced dopamine release remained robust in VS. In sum, whereas taste quality regulates dopamine release in ventral striatum, increases in dopamine release in dorsal striatum appear to be under strict metabolic control.

Because quantifying dopamine release provides what is essentially a correlative measure, it is critical to assess how sweetness and nutritional signals impact on striatal neurons expressing dopamine receptors. Briefly, striatal neurons express either one of two types of dopamine receptors, "D1" or "D2" [13]. Dopamine is known to specifically increase the excitability of D1r-expressing neurones [20,21], implying that D1r-expressing neurons in VS and DS increase excitability during the ingestion of sweet and/or nutritive sugars.

Tellez et al. [10] assessed the effects of specifically ablating dopamine-excitable D1r-neurones in DS or VS. This was achieved by virally introducing a Cre-dependent caspase into striatal neurons of D1r-Cre mice. In agreement with the dialysis results above, ablating dopamine-excitable D1r-expressing cells in ventral striatum caused mice to display greater aversion to a sweet-bitter mixture, suggesting lower sensitivity to the masking effects of the sweet component. In contrast, ablating D1r-expressing cells in dorsal striatum did not produce any clear effects. However, symmetrical results were obtained upon performing the converse

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