Published in final edited form as:

Physiol Behav. 2016 October 1; 164(Pt B): 473–477. doi:10.1016/j.physbeh.2016.04.041.

Circuit Organization of Sugar Reinforcement

Ivan E de Araujo

The John B Pierce Laboratory, New Haven CT, USA

Department of Psychiatry, Yale University School of Medicine, New Haven CT, USA

Department of Physiology, Yale University School of Arts and Sciences, New Haven CT, USA

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.

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 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 minutes, 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

Ivan E de Araujo, DPhil, The John B. Pierce Laboratory & Yale University School of Medicine, 290 Congress Avenue, New Haven CT 06519, USA, Phone: +1 (203) 5629901 x204, Fax: +1 (203) 6244950, IAraujo@jbpierce.org, ivan.araujo@yale.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

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 pre-specified 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.

Separate Dopaminergic Pathways Encode Gustatory and Nutritional Values of Sugar

I. 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, synthesized 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 nonmetabolizable 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 experiment, where hungry mice were presented with a bitter solution that was paired to increasing concentrations of intra-gastric glucose. In this preparation, once the concentration of the intra-gastric glucose was sufficiently high, only dorsally-ablated mice failed to increase licking for the bitter solution in order to obtain intra-gastric sugar. In other words, in the presence of a non-palatable yet nutritive food source, dorsally-ablated mice ended up poorly nourished when compared to ventrally-ablated or control mice.

Interestingly, the above phenomenon still holds when a flavour-nutrient paradigm was employed. Hungry mice were exposed to one-bottle learning sessions where licks for a sweet solution were paired to intra-gastric infusions of the non-nutritive sweetener, whereas licks for a bitter solution were paired to intra-gastric infusions of the nutritive glucose. All mice shifted preferences towards the bitter yet nutritive stimulus, with the exception of dorsally-ablated mice, which continued to prefer the non-nutritive but sweeter solution. In sum, VS and DS D1r-expressing populations separately mediate the gustatory and nutritional actions of sugar.

These loss-of-function studies were next complemented by gain-of-function experiments where VS and DS D1r-expressing neurons were specifically depolarized using optogenetic techniques. More precisely, a Cre-dependent light-sensitive cation channel was virally delivered into the VS and DS of D1r-Cre mice [22, 23]. Using such tools, Tellez *et al.* [10] tested the hypothesis that artificial activation of D1r-neurones in DS would substitute for sugar during the ingestion of unpalatable adulterated sweeteners.

During the optogenetic experiments, mice licked a sweet solution, such that detected licks triggered, instead of intra-gastric infusions, light pulses to VS or DS. These optogenetic studies produced effects that are largely consistent with the notion of separate roles for VS and DS D1r-expressing neurons in encoding gustatory and nutritional sugar values. Specifically, optogenetic stimulation of D1r-neurones in VS enhanced sweet taste ingestion but failed to attenuate the aversive effects produced by adding a bitter tastant. However, and rather remarkably, stimulation of DS D1r-neurones not only increased sweet intake, but also completely annulled the suppressive effects of the bitter tastant. In sum, activation of a dual

dopamine-controlled striatal system is necessary and sufficient to regulate appetitive responses to gustatory *vs.* nutritional cues generated by sugar.

II. *Drosophila*

Strikingly, this trait appears to be conserved in invertebrates. First, it is remarkable that, likewise rodents, *Drosophila* flies display strong preferences for D- *vs.* L-glucose independently of sweet receptor activity [24]. The ability of the fly brain to separate sweet *vs.* post-ingestive signals is corroborated by the fact that sweetness and nutrient value respectively reinforce short- and long-term memories in flies [25-28] – attesting for the primacy of energy-seeking over taste quality.

The homology with the rodent case goes even further, as neuronal activity in *Drosophila* dopaminergic neurons is associated with a delayed calcium trace that appears to represent the integration of chemosensory information with post-ingestive energetic value [27]. Such model delineates a dopaminergic-dependent mechanism by which short-lived chemosensation can be associated with post-ingestive factors, as is the requirement for effective flavor-nutrient-conditioning. Note that the delayed calcium trace in dopamine cells reported by Musso *et al.* [27] appears as functionally equivalent to the chronic rises in dopamine levels produced by intra-gastric sugar infusions observed in our own studies [9, 10, 19, 29, 30].

The case for a dopamine-controlled mechanism regulating sugar preferences in *Drosophila* is further strengthened by recent findings reporting that sweet taste and nutrient value recruit different populations of dopaminergic neurons [25, 26, 28]. Very interestingly, and in striking homology to the ventral *vs.* dorsal dopamine pathways of rodents, the sweet- and nutrient-sensitive dopamine neurons of flies were found to project to segregated downstream targets. Huetteroth *et al.* [26] showed that sweet taste initially engages octopaminergic neurons; octopamine, in turn, acts through the OAMB receptor to activate OAMB-expressing rewarding dopaminergic neurons that innervate β'_{2am} and γ_4 regions of the mushroom body. In contrast, the formation of nutrient-dependent long-term memories was found to require an entirely separable population of dopaminergic neurons, namely, those projecting to the γ_{5b} regions. Interestingly, Huetteroth *et al.* also showed that whereas artificial implantation and expression of short-term memory occur in satiated flies, formation and expression of artificial long-term memory require flies to be hungry. These results confirm and further extend previous findings linking octopaminergic *vs.* dopaminergic neuronal populations to the formation of taste- *vs.* nutrient-driven memories [25].

Dissection of dopaminergic circuit function also leads to determining the genetic identity of those dopamine neurons mediating sweet- or nutrient-driven memories. Studying a specific cluster of dopamine neurons (“PAM” neurons) in the fly brain, Yamagata *et al.* [28] established that the reinforcement properties of sweetness and nutrition are independently conveyed to distinct subclusters of the PAM cluster. Specifically, whereas octopamine-expressing neurons regulated the dopaminergic PAM subcluster associated with sweetness-driven reinforcement, Gr43a neurons targeted the dopaminergic PAM subcluster associated with nutrient-driven reinforcement, namely, PAM- $\alpha 1$ neurons. Interestingly, the temporal

dynamics of short- vs. long-term memory components were found to act complementarily, resulting in the formation of stable memory retention.

What comes next?

In sum, a novel picture of sugar reward emerges, where separate sensorimotor circuits mediate the dissociable reinforcing effects of orosensory sweetness and gut nutritional cues. These circuits are placed under the ultimate control of separable populations of dopamine-producing neurons in the brains of both flies and rodents, suggesting that specialized dopaminergic subpopulations form a class of evolutionary conserved chemo- and nutrient-sensors (See schematics in Figure 1).

Two major questions remain however unanswered in both rodent and fly models. They refer to the downstream and upstream effectors of the nutrient-sensing dopaminergic cells. Regarding the downstream circuitry, one must ask how does dopamine modulation of striatal/mushroom body neurons ultimately translate into the execution of motor consummatory programs. Current evidence indicates that the execution of such programs is separately controlled by gustation and nutrition, as prototypically exemplified by greater increases in bitter intake when the aversive taste is paired to intra-gastric glucose [10]. In rodents, this may be achieved via the releasing of brainstem premotor centers from tonic inhibition by downstream striatal targets [31] such as the *Substantia Nigra, pars reticulata* [32]. A similar model may apply to the case of flies. It has been reported that dopamine modulates proboscis extension to sugar in *Drosophila*, such that artificial silencing or activation of dopamine neurons bidirectionally regulate proboscis activity [33]. This is achieved via extensive branching of one dopaminergic neuron in the subesophageal ganglion, where some of the motor neurons that drive proboscis extension reside [33]. Future research must identify the neuronal targets of dopamine clusters linking taste-independent energy sensing to motor circuits controlling buccal muscles in vertebrates and invertebrates alike.

Second, the identity of the reward-driving D-glucose sensor remains elusive – not to mention the fact that it remains unclear if such sensor ultimately resides in the periphery or in the central nervous system. Recent work from our laboratory, making use of mouse models of bariatric interventions, reveals an important impact of gastrointestinal rerouting on striatal dopaminergic efflux [29]. This strengthens current evidence favoring a central role for duodenal nutrient influx in dopamine-mediated preference behaviors [34, 35]. However, future research must identify the physiological pathways that ultimately link duodenal nutrient sensing to dopamine efflux. Hypothetical models that must be evaluated include not only the activity of intestinal glucose sensors/cotransporters such as SGLTs [36], but also a potential role for post-absorptive metabolic sensing. In fact, small infusions of intra-portal, but not intra-jugular, D-glucose produced robust dopamine release in dorsal striatum [29]. This is consistent with the notion that glucose, upon duodenal transport, activates metabolic sensors residing within the portal-mesenteric system [37, 38]. In flies, recent accounts identified novel sugar-sensing candidates residing in the *Drosophila* brain. Specifically, six neurosecretory cells producing the Diuretic hormone 44 (Dh44, a homolog of the mammalian corticotropin-releasing hormone) were specifically activated by nutritive sugars

like D-glucose [39]. In fact, disrupting the firing activity of these neurons (or the expression of Dh44) resulted in a failure to select D-glucose over nonnutritive L-glucose [39]. A massive effort lying ahead thus relates to the dissection of the circuitry linking portal-mesenteric/Dh44 neural pathways to brain dopaminergic clusters.

Acknowledgment

This work was supported by NIH grants R01DC014859 and R01CA180030.

References

1. Hu FB. Resolved: there is sufficient scientific evidence that decreasing sugar-sweetened beverage consumption will reduce the prevalence of obesity and obesity-related diseases. *Obes Rev.* 2013; 14(8):606–19. [PubMed: 23763695]
2. Wang DD, et al. Trends in dietary quality among adults in the United States, 1999 through 2010. *JAMA Intern Med.* 2014; 174(10):1587–95. [PubMed: 25179639]
3. Watts AG, Donovan CM. Sweet talk in the brain: Glucosensing, neural networks, and hypoglycemic counterregulation. *Frontiers in Neuroendocrinology.* 2009; 31:32–43.
4. Newsholme EA. The glucose/fatty acid cycle and physical exhaustion. *Ciba Found Symp.* 1981; 82:89–101. [PubMed: 6913480]
5. Yarmolinsky DA, Zuker CS, Ryba NJ. Common sense about taste: from mammals to insects. *Cell.* 2009; 139(2):234–44. [PubMed: 19837029]
6. Mueller KL, et al. The receptors and coding logic for bitter taste. *Nature.* 2005; 434(7030):225–229. [PubMed: 15759003]
7. Holman GL. Intragastric reinforcement effect. *J Comp Physiol Psychol.* 1968; 69:432–41. [PubMed: 5349026]
8. Sclafani A. Post-ingestive positive controls of ingestive behavior. *Appetite.* 2001; 36(1):79–83. [PubMed: 11161347]
9. de Araujo IE, et al. Food reward in the absence of taste receptor signaling. *Neuron.* 2008; 57(6):930–41. [PubMed: 18367093]
10. Tellez LA, et al. Separate circuitries encode the hedonic and nutritional values of sugar. *Nat Neurosci.* 2016; 19(3):465–70. [PubMed: 26807950]
11. Stephenson-Jones M, et al. Independent circuits in the basal ganglia for the evaluation and selection of actions. *Proc Natl Acad Sci U S A.* 2013; 110(38):E3670–9. [PubMed: 24003130]
12. Everitt BJ, Robbins TW. Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nat Neurosci.* 2005; 8(11):1481–9. [PubMed: 16251991]
13. Gerfen CR, Surmeier DJ. Modulation of striatal projection systems by dopamine. *Annu Rev Neurosci.* 2011; 34:441–66. [PubMed: 21469956]
14. Grillner S, Robertson B, Stephenson-Jones M. The evolutionary origin of the vertebrate basal ganglia and its role in action selection. *J Physiol.* 2013; 591(Pt 22):5425–31. [PubMed: 23318875]
15. Yin HH, Ostlund SB, Balleine BW. Reward-guided learning beyond dopamine in the nucleus accumbens: the integrative functions of cortico-basal ganglia networks. *Eur J Neurosci.* 2008; 28(8):1437–48. [PubMed: 18793321]
16. Wickens JR, et al. Dopaminergic mechanisms in actions and habits. *J Neurosci.* 2007; 27(31):8181–3. [PubMed: 17670964]
17. Palmiter RD. Dopamine signaling in the dorsal striatum is essential for motivated behaviors: lessons from dopamine-deficient mice. *Ann N Y Acad Sci.* 2008; 1129:35–46. [PubMed: 18591467]
18. Yelnikoff L, et al. An update on the connections of the ventral mesencephalic dopaminergic complex. *Neuroscience.* 2014; 282C:23–48. [PubMed: 24735820]
19. Ren X, et al. Nutrient Selection in the Absence of Taste Receptor Signaling. *J Neurosci.* 2010; 30:8012–8023. [PubMed: 20534849]

20. Ericsson J, et al. Dopamine differentially modulates the excitability of striatal neurons of the direct and indirect pathways in lamprey. *J Neurosci*. 2013; 33(18):8045–54. [PubMed: 23637194]
21. Planert H, Berger TK, Silberberg G. Membrane properties of striatal direct and indirect pathway neurons in mouse and rat slices and their modulation by dopamine. *PLoS One*. 2013; 8(3):e57054. [PubMed: 23469183]
22. Kravitz AV, Tye LD, Kreitzer AC. Distinct roles for direct and indirect pathway striatal neurons in reinforcement. *Nat Neurosci*. 2012; 15(6):816–8. [PubMed: 22544310]
23. Lobo MK, et al. Cell type-specific loss of BDNF signaling mimics optogenetic control of cocaine reward. *Science*. 2010; 330(6002):385–90. [PubMed: 20947769]
24. Dus M, et al. Taste-independent detection of the caloric content of sugar in *Drosophila*. *Proc Natl Acad Sci U S A*. 2011; 108(28):11644–9. [PubMed: 21709242]
25. Burke CJ, et al. Layered reward signalling through octopamine and dopamine in *Drosophila*. *Nature*. 2012
26. Huetteroth W, et al. Sweet taste and nutrient value subdivide rewarding dopaminergic neurons in *Drosophila*. *Curr Biol*. 2015; 25(6):751–8. [PubMed: 25728694]
27. Musso PY, Tchenio P, Preat T. Delayed dopamine signaling of energy level builds appetitive long-term memory in *Drosophila*. *Cell Rep*. 2015; 10(7):1023–31. [PubMed: 25704807]
28. Yamagata N, et al. Distinct dopamine neurons mediate reward signals for short- and long-term memories. *Proc Natl Acad Sci U S A*. 2015; 112(2):578–83. [PubMed: 25548178]
29. Han W, et al. Striatal Dopamine Links Gastrointestinal Rerouting to Altered Sweet Appetite. *Cell Metabolism*. 2016 In Press.
30. Tellez LA, et al. Glucose utilization rates regulate intake levels of artificial sweeteners. *J Physiol*. 2013; 591(Pt 22):5727–44. [PubMed: 24060992]
31. Wurtz RH, Hikosaka O. Role of the basal ganglia in the initiation of saccadic eye movements. *Prog Brain Res*. 1986; 64:175–90. [PubMed: 3523602]
32. Shammah-Lagnado SJ, Costa MS, Ricardo JA. Afferent connections of the parvocellular reticular formation: a horseradish peroxidase study in the rat. *Neuroscience*. 1992; 50(2):403–25. [PubMed: 1279462]
33. Marella S, Mann K, Scott K. Dopaminergic modulation of sucrose acceptance behavior in *Drosophila*. *Neuron*. 2012; 73(5):941–50. [PubMed: 22405204]
34. Ackroff K, Yiin YM, Sclafani A. Post-oral infusion sites that support glucose-conditioned flavor preferences in rats. *Physiol & Behav*. 2010; 99:402–11. [PubMed: 20026145]
35. de Araujo IE, et al. The gut-brain dopamine axis: A regulatory system of caloric intake. *Physiol & Behav*. 2012; 106:394–9. [PubMed: 22406348]
36. Zukerman S, Ackroff K, Sclafani A. Post-oral appetite stimulation by sugars and nonmetabolizable sugar analogs. *Am J Physiol Regul Integr Comp Physiol*. 2013; 305(7):R840–53. [PubMed: 23926132]
37. Bohland M, et al. Activation of hindbrain neurons is mediated by portal-mesenteric vein glucosensors during slow-onset hypoglycemia. *Diabetes*. 2014; 63(8):2866–75. [PubMed: 24727435]
38. Delaere F, et al. Portal glucose influences the sensory, cortical and reward systems in rats. *Eur J Neurosci*. 2013; 38(10):3476–86. [PubMed: 24011250]
39. Dus M, et al. Nutrient Sensor in the Brain Directs the Action of the Brain-Gut Axis in *Drosophila*. *Neuron*. 2015; 87(1):139–51. [PubMed: 26074004]

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.

Figure 1. Separate gustatory and nutrient-sensing dopamine pathways control sugar reward in rodents and flies

A. In vertebrates (mice), separate ventral (red lines) and dorsal (blue lines) dopamine pathways encode the gustatory and nutritional values of sugar. This model (after Tellez *et al*) is consistent with the animal's ability to persist licking an aversive solution whenever this solution is associated with energy gain. Connections ending as triangles represent excitatory/modulatory connections. Connections ending as simple trace represent inhibitory connections, as based on current knowledge of the chemical structure of these pathways.

DA=Dopamine, DS=Dorsal striatum, SNc=*Substantia Nigra, pars compacta*, SNr=*Substantia Nigra, pars reticulata*, VP=Ventral pallidum, VS=Ventral striatum.

B. In invertebrates (flies), separate ventral (red lines) and dorsal (blue lines) dopamine pathways also encode the gustatory and nutritional values of sugar. In this model, gustatory sweetness activates octopamine neurons upstream of a subcluster of dopaminergic cells (Burke *et al.*, Huetteroth *et al.*, Yamagata *et al.*), possibly PAM cluster neurons (Yamagata *et al.*) expressing octopamine receptor OAMB (Huetteroth *et al.*). Nutritional cues, in turn, activate Gr43-expressing neurons upstream of a subcluster of dopaminergic cells (Burke *et al.*, Huetteroth *et al.*, Yamagata *et al.*), possibly PAM- $\alpha 1$ neurons (Yamagata *et al.*). Whereas sweet-sensitive dopamine neurons appear to terminate in the β'_{2am} and γ_4 regions of the mushroom body, nutrient-sensitive dopamine neurons terminate in the γ_{5b} regions (Huetteroth *et al.*). Importantly, activity in this latter pathway is regulated (potentiated) by hunger. DA=Dopamine, Gr43=Gustatory receptor 43, OAMB+=OAMB-expressing dopamine cells, OCT=octopamine.