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Review Article

Shared neurocircuitry underlying feeding and drugs of abuse in *Drosophila*

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ABSTRACT

The neural circuitry and molecules that control the rewarding properties of food and drugs of abuse appear to partially overlap in the mammalian brain. This has raised questions about the extent of the overlap and the precise role of specific circuit elements in reward and in other behaviors associated with feeding regulation and drug responses. The much simpler brain of invertebrates including the fruit fly *Drosophila*, offers an opportunity to make high-resolution maps of the circuits and molecules that govern behavior. Recent progress in *Drosophila* has revealed not only some common substrates for the actions of drugs of abuse and for the regulation of feeding, but also a remarkable level of conservation with vertebrates for key neuromodulatory transmitters. We speculate that *Drosophila* may serve as a model for distinguishing the neural mechanisms underlying normal and pathological motivational states that will be applicable to mammals.

In all animals, hunger drives the motivation to seek out food. Peripheral hormones directly regulate food seeking, and the targets of these peripheral hunger and satiety signals have been mapped to distinct hypothalamic and hindbrain nuclei in mammals [1]. Satiety signals and homeostatic brain circuits that limit feeding can be overridden by highly palatable food irrespective of the animal's nutritional state [2]. For example, remote manipulation of feeding circuits in mice and the fruit fly *Drosophila* promotes voracious eating in lieu of satiety signals [3,4]. In other words, organisms as distinct as mammals and invertebrates may have evolved common and hard-wired central feeding circuits in the brain.

Drugs of abuse have the capacity to evoke highly motivated and goal-directed behavior with an intensity that can eclipse even that of a very hungry animal [5]. Addictive drugs such as cocaine and alcohol have reinforcing properties similar to food, and their pleiotropic actions are mediated in part by highly complex reward circuitry, such as the drug and feeding-engaged mesolimbic dopaminergic pathways [6]. Despite some commonalities in behavioral states and implicated brain circuitry, direct functional overlap of specific circuit elements has been difficult to prove, partly because of the ever-more appreciated complexity of the brain, but also because the quality and interpretation of behavioral measurements are rapidly improving [7].

Drosophila is an attractive model organism for conjoining behavioral, neuroanatomical, and genetic studies, because of its genetic tractability, the development of precise and high

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throughput assays, and the availability of tools to manipulate neuronal properties in a spatiotemporally accurate manner [8]. Remarkably, homeostatic metabolic systems and neurochemical circuit motifs in mammals and *Drosophila* appear to be largely conserved [9,10]. Circuit and neuron-specific manipulation in fruit flies has permitted the investigation of genetic and molecular targets that underlie the complex actions of addictive drugs as well as the homeostatic signals that regulate feeding [9,10].

Here, we review recent findings indicating that the regulation of feeding and the neural mechanisms of drugs of abuse in fruit flies may have significant overlap. We limit our scope to common neuromodulators and circuitry including dopamine, the amines tyramine and octopamine, the neuropeptide Y (NPY)-like neuropeptide F (NPF), the eight *Drosophila* insulin-like peptides (DILPs), and the neuropeptide corazonin. We include molecular and circuit-level descriptions for some drug-related behaviors that may be distinct from reward and motivation, but that appear to share some common elements with feeding. More comprehensive reviews on the regulation of feeding and on the molecular and behavioral actions of drugs of abuse in *Drosophila* were published recently [9,11,12].

Dopamine

Dopamine is a pleiotropic modulator of behavior in mammals and in fruit flies: depending on the behavioral context, dopamine in *Drosophila* affects sleep, mating, learning and memory, locomotion, feeding, and the effects of drugs of abuse [13–17]. There are approximately 280 dopaminergic neurons in the adult fly brain that are subdivided into eight major clusters based on their cell body location, and each cluster sends projections to distinct brain regions [Fig. 1] [18,19]. Dopamine signaling is detected by four receptors that are distributed broadly in the brain: the D1-like receptors DopR1 (DA1, DopR) and DopR2 (DAMB), the multiply spliced D2-like receptor D2R, and the DopEcR receptor that is also gated by the insect hormone ecdysone [20]. Emerging evidence indicates that particular dopamine clusters and even individual neurons likely form valence-specific circuit motifs that are engaged by conditioned or innate values of a stimulus, and whose function can be modified by the internal state [16,21–24].

Dopamine in feeding behaviors

Feeding behaviors are subdivided into six distinct phases: foraging/seeking, cessation of locomotion, meal initiation, consumption, meal termination, then finally food disengagement [11]. The feeding behaviors we discuss are complex and can overlap between two or more of the respective phases of feeding. A portion of our focus will encompass behavioral assays that assess goal-directed approach or avoidance behavior in the context of both unconditioned and conditioned food-related stimuli. The study of goal-directed approach or avoidance is a method to evaluate the relationship between valence-specific circuit motifs and innate/learned feeding motivation [16].

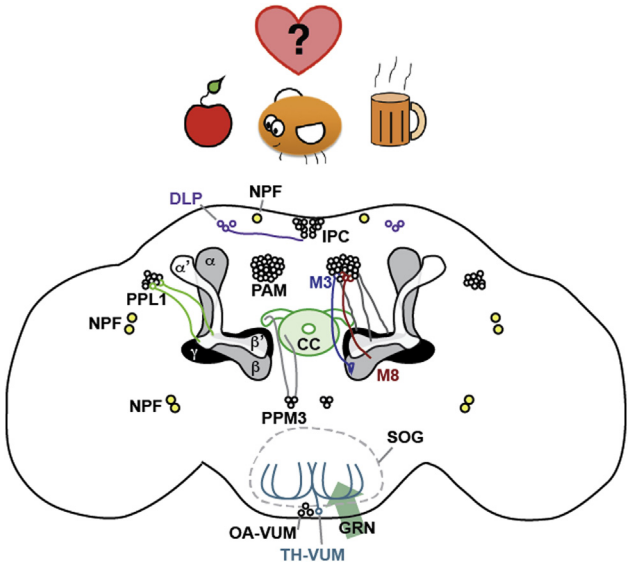

Fig. 1 – Schematic of the Drosophila adult brain. The diagram depicts the major neuropils and cell types discussed in this review, except for the mushroom body output neurons (MBON) that are excluded for purposes of clarity. All structures are bilaterally symmetric except for the ventral unpaired medial cells that are octopaminergic (OA-VUM) or dopaminergic (TH-VUM). Gustatory information is carried into the brain by gustatory receptor neurons (GRN) that terminate in the SOG. The TH-VUM makes an elaborate tree-like arborization in the SOG. The mushroom bodies are comprised of α/α′, β/β′, and γ lobes. The protocerebral anterior medial (PAM), protocerebral posterior lateral 1 (PPL1), and protocerebral posterior medial 3 (PPM3) clusters are all dopaminergic. The PAM and PPL1 neurons innervate distinct regions of the mushroom bodies and make both ipsilateral and contralateral (not shown) connections. The MBONs send dopamine/mushroom body information to protocerebral integration centers near the mushroom bodies. Individual PPM3 neurons innervate the ellipsoid body (doughnut) and fan-shaped body of the central complex (CC). The insulin-producing cells (IPC) of the pars intercerebralis neuroendocrine gland extend processes (not shown) medially to regions of the brain above the SOG and out of the brain to endocrine organs and other targets. The dorsal lateral protocerebral (DLP) cells express corazonin and extend processes to the IPC.

Protocerebral anterior medial neurons

Most fruit fly dopamine neurons, about 130 per hemisphere, are located in the protocerebral anterior medial (PAM) cluster. The PAM neurons densely innervate the mushroom bodies, prominent brain structures implicated in associative learning and memory and other behaviors. The mushroom bodies are composed of approximately 2500 Kenyon cells per hemisphere that are named α/α′, β/β′, and γ based on anatomical division [Fig. 1]. The PAM presynaptic terminals contact discrete regions in the β, β′, and γ lobes that comprise the