

Dopamine as a Multifunctional Neurotransmitter in Gastropod Molluscs: An Evolutionary Hypothesis

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Abstract. The catecholamine 3,4-dihydroxyphenethylamine, or dopamine, acts as a neurotransmitter across a broad phylogenetic spectrum. Functions attributed to dopamine in the mammalian brain include regulation of motor circuits, valuation of sensory stimuli, and mediation of reward or reinforcement signals. Considerable evidence also supports a neurotransmitter role for dopamine in gastropod molluscs, and there is growing appreciation for its potential common functions across phylogeny. This article reviews evidence for dopamine's transmitter role in the nervous systems of gastropods. The functional properties of identified dopaminergic neurons in well-characterized neural circuits suggest a hypothetical incremental sequence by which dopamine accumulated its diverse roles. The successive acquisition of dopamine functions is proposed in the context of gastropod feeding behavior: (1) sensation of potential nutrients, (2) activation of motor circuits, (3) selection of motor patterns from multifunctional circuits, (4) valuation of sensory stimuli with reference to internal state, (5) association of motor programs with their outcomes, and (6) coincidence detection between sensory stimuli and their consequences. At each stage of this sequence, it is proposed that existing functions of dopaminergic neurons favored their recruitment to fulfill additional information processing demands. Common functions of dopamine in other intensively studied groups, ranging from mammals and insects to nematodes, suggest an ancient origin for this progression.

Introduction

Dopamine (DA) is arguably the most intensively studied neurotransmitter, with a query of PubMed yielding more than 5000 citations for the year 2019. In the mammalian brain, dopaminergic signaling participates in functions ranging from lactation to higher cognitive operations (Iversen *et al.*, 2010; Di Chiara *et al.*, 2014). However, 2 archetypal functions of DA, initially reported nearly 50 years ago, have withstood the test of time. Its involvement in motor control originally emerged from clinical observations (Barbeau, 1967, 1974; Hornykiewicz, 1973, 1982), and its pivotal role in reward-related signaling was established in studies on animal learning and memory (Yokel and Wise, 1975; Wise and Rompré, 1989; Wise, 2004, 2008; Schultz, 2007, 2010).

Many neurotransmitters, including DA, are widely conserved across animal taxa (Kehoe and Marder, 1976; Strausfeld and Hirth, 2013; Fieber, 2017). In his highly influential review of the early literature on invertebrate neurotransmitters, Gerschenfeld (1973, p. 74) concluded that the evidence for DA as a neurotransmitter in molluscs remained “rather indirect and circumstantial.” Subsequent neuroanatomical, biochemical, pharmacological, and physiological findings resolved this uncertainty and firmly established DA as a gastropod neurotransmitter (reviewed by Kerkut, 1973; Walker and Kerkut, 1978; Walker, 1986). This foundation set the stage for exploring dopaminergic signaling in well-characterized neuronal circuits that produce gastropod behavior. This article surveys the diverse contributions of DA signaling to gastropod sensorimotor integration and plasticity, with an emphasis on its functions that are shared by other complex nervous systems (see Barron *et al.*, 2010; Gillette and Brown, 2015). A hypothetical sequence charting the acquisition of functions by dopaminergic neurons suggests that each role favored its recruitment into successive information processing tasks. The presence of common functions of DA across a broad range of taxa implies

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Abbreviations: BMP, buccal motor program; cAMP, 3', 5'-cyclic adenosine monophosphate; CBI, cerebral-buccal interneuron; CNS, central nervous system; CPG, central pattern generator; DA, dopamine; En.2, esophageal nerve branch; EPSP, excitatory postsynaptic potential; GDC, giant dopaminergic cell; Mya, million years ago; PRN, pattern reversing neuron; THli, tyrosine hydroxylase-like immunoreactive.

that this proposed sequence could reflect an ancient prototype that has been implemented to varying degrees in different groups.

Histochemical, Biochemical, and Pharmacological Foundations

The histochemical fluorescence method of Falck and Hil-larp (Falck *et al.*, 1962) was initially used to demonstrate the presence of catecholamines in neurons of the cerebral, pedal, and visceral ganglia of *Helix pomatia* (Dahl *et al.*, 1962, 1966). The green fluorescence indicative of DA was also observed in the central nervous systems of *Tritonia diomedea* (Sakharov *et al.*, 1965; Sakharov and Zs-Nagy, 1968), *Planorbis corneus* (Marsden and Kerkut, 1970), *Strophocheilus oblongus* (Jaeger *et al.*, 1971), *Limax maximus* (Osborne and Cottrell, 1971), *Biomphalaria glabrata* (Chiang *et al.*, 1974), and *Hermisenda crassicornis* (Croll, 1987). These observations were corroborated by fluorometric and chromatographic measurements (Cardot, 1963; Sweeney, 1963; Kerkut *et al.*, 1966, 1967; Osborne and Cottrell, 1970; Juorio and Killick, 1972; Straub and Kuhlman, 1984; Hetherington *et al.*, 1994; Manger *et al.*, 1996).

Early pharmacological studies demonstrated excitatory and inhibitory responses to bath application of DA in neurons of *Cornu (Helix) aspersum* (Kerkut and Walker, 1961, 1962; Walker *et al.*, 1968; Woodruff and Walker, 1969) and inhibitory effects in the Argentine land snail *Crytomphallus aspersa* (Gerschenfeld, 1964). More precise application of drugs using microiontophoresis enabled Ascher (1968, 1972) to show that some neurons of *Aplysia* possess both excitatory and inhibitory DA receptors. Swann and Carpenter (1975) observed common properties between responses to DA and acetylcholine in *Aplysia* neurons and proposed that the receptors for both transmitters were associated with common Na^+ , Cl^- , and K^+ ionophores (see also Yavari *et al.*, 1979; Ascher and Chesnoy-Marchais, 1982). Several studies tested the efficacy of agonists and antagonists on gastropod DA receptors, with particular attention to their possible utility for screening potential therapeutic compounds; but the pharmacological profiles of the gastropod DA receptors were found to differ from their vertebrate counterparts (reviewed by Woodruff, 1971; Gospe, 1983; Walker, 1986).

Some actions of DA in gastropod nervous systems are long lasting and reflect activation of second messenger signaling cascades. Cedar and Schwartz (1972) showed that DA and serotonin, but not carbachol, glutamate, or norepinephrine, increased levels of 3', 5'-cyclic adenosine monophosphate (cAMP) in *Aplysia* nervous tissue. In specific neurons of *Cornu (Helix) aspersum*, DA and serotonin both produced a decreased K^+ conductance and had additive stimulatory effects on adenylate cyclase activity, indicating that their signaling converged at the second messenger level (Deterre *et al.*, 1982). Additional second messenger-mediated actions of

DA were demonstrated on K^+ and Ca^{++} currents that contribute to somatic action potentials in identified *Cornu (Helix) aspersum* neurons (Paupardin-Tritsch *et al.*, 1985).

Dopamine was also found to regulate slow voltage-dependent currents in *Aplysia* neurons. In the endogenous bursting cell R15, DA eliminated bursting by reducing the regenerative inward current underlying slow oscillations of the membrane potential (Wilson and Wachtel, 1978). In RB neurons of the *Aplysia* abdominal ganglion, DA augmented a voltage-dependent calcium current that was activated at holding potentials more positive than -40 mV and maximal near 0 mV (Pellmar, 1981b). This current was also elicited by serotonin and octopamine and by injection of cAMP, suggesting convergence at the level of the second messenger (Pellmar and Carpenter, 1980, 1981; but see Pellmar, 1981a). Enhancement of the voltage-dependent calcium current by neurotransmitters was proposed as a mechanism by which heterosynaptic modulation could alter action potentials or slow waves that underlie bursting (Pellmar and Carpenter, 1980).

A role for DA at gastropod central synapses was supported by studies on a prolonged inhibitory postsynaptic potential (inhibition of long duration) produced in specific neurons in response to nerve stimulation. Dopamine produced hyperpolarizing responses in neurons that exhibited inhibition of long duration; and ergonovine, a DA antagonist, blocked both the synaptic and DA responses (Kerkut *et al.*, 1969; Walker *et al.*, 1971; Boisson and Gola, 1976). Thus, together with the histological and pharmacological findings reviewed above, there was abundant support for the role of DA as a neurotransmitter in the gastropod central nervous system (CNS) prior to the identification of dopaminergic neurons.

Dopaminergic Regulation of Peripheral Systems

The involvement of DA in peripheral signaling was initially examined in the gill of *Aplysia californica* due to its participation in simple forms of learning (Peretz and Estes, 1974; Kebabian *et al.*, 1979). High levels of DA were measured in the gill, and paraformaldehyde-induced green fluorescence was observed in neurons along the peripheral nerve trunks (Carpenter *et al.*, 1971; Peretz and Estes, 1974). The observation that DA enhanced contractions produced by non-dopaminergic gill motor neurons appears to be the first instance in which its actions were described as modulatory (Swann *et al.*, 1978a, b). Perfusion of the gill with micromolar concentrations of DA also decreased the habituation of responses to repeated motor neuron stimuli (Ruben and Lukowiak, 1979, 1983).

Tritt and Byrne (1982) examined the potential role of DA in control of the opaline gland of *A. californica*. Infusion of DA through a branch of the anterior aorta produced opaline gland contractions that were blocked by fluphenazine. Dopamine also increased the amplitude of excitatory junction potentials and contractions produced by stimulation of three

motor neurons in the pleural ganglion. Dopamine was proposed to act as both a neurotransmitter and as a neuromodulator in the *Aplysia* opaline gland (Tritt and Byrne, 1982). The source of DA innervation of the opaline gland remained unspecified, however, because the glyoxylic acid technique did not produce fluorescence in the identified central motor neurons (Tritt *et al.*, 1983).

Finally, histochemical fluorescence and microspectrofluorometric observations led to a proposed role for DA in regulating the female reproductive system of gastropods (Hartwig *et al.*, 1980). Using formaldehyde histofluorescence, a plexus of intraepithelial cells was detected in the duct of the albumen gland of the pond snail *Bulinus truncatus* and the carrefour of the land snail *Archachatina marginata*. Microspectrofluorometry confirmed the presence of DA in these tissues (Hartwig *et al.*, 1980). In *Helisoma duryi*, tyrosine hydroxylase-like immunoreactive (THli) axons were shown to form a nerve tract in the central region of the albumen gland and a uniform network of fibers spreading over the entire gland (Kiehn *et al.*, 2001). Recently, we detected a network of THli neurons in the albumen gland of *Bursatella leachii* (ragged sea hare, Fig. 1), a marine gastropod (Ramos *et al.*, 1995; Miller, 1997). This observation broadens the potential involvement of DA in female reproductive function to the Euopisthobranchia.

Application of DA to the albumen gland of *Helisoma duryi* and *Biomphalaria glabrata* stimulated glycoprotein secretion

(Saleuddin *et al.*, 2000; Santhanagopalan and Yoshino, 2000; Mukai *et al.*, 2004). Moreover, DA levels were increased in the albumen glands of *B. glabrata* during the initial stage of egg production, when perivitelline fluid is being secreted around each ovum (Boyle and Yoshino, 2002). The intrinsic dopaminergic network was proposed to coordinate fluxes between the albumen gland and the carrefour, where fertilized eggs are coated (Boyle and Yoshino, 2002; see also Brisson, 1983; de Jong-Brink and Goldschmeding, 1983). Collectively, the functions of DA on the gill, opaline gland, and albumen gland established its role in the regulation of gastropod peripheral systems.

Dopamine as a Sensory Neurotransmitter

In gastropods that have been studied, the number of peripheral dopaminergic neurons far exceeds the total present in the CNS (Croll, 2001; Croll *et al.*, 2003). Peripheral catecholaminergic innervation of the integument was initially reported in *Biomphalaria glabrata* (Chiang *et al.*, 1974), *Aplysia depilans* and *Aplysia fasciata* (Salimova *et al.*, 1987a), and *Cornu (Helix) aspersum* (Hernádi and Elekes, 1999). More refined techniques enabled Croll (2001; Croll *et al.*, 2003) to detect thousands of THli neurons with subepithelial somata and processes that penetrate the overlying body wall in *Aplysia californica*. Axons from these cells project centrally via the major nerves and terminate diffusely in all ganglia, supporting

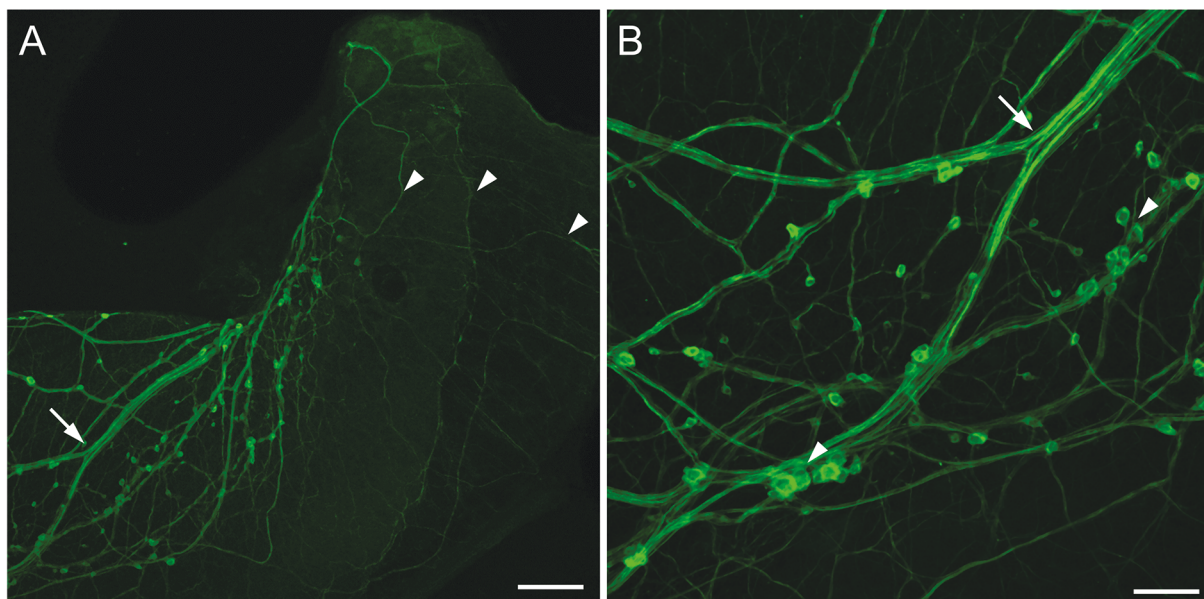


Figure 1. Tyrosine hydroxylase-like immunoreactivity in the albumen gland of *Bursatella leachii*. (A) Low-power image showing bundles of tyrosine hydroxylase-like immunoreactive (THli) fibers (arrow) entering the albumen gland. Small immunoreactive somata were observed adhering to the fiber tracts. Fine axons (arrowheads) covered the entire surface of the gland. Scale bar = 200 μ m. (B) At higher magnification, some of the small (5–10- μ m-diameter) THli cell bodies were solitary, and others were clustered into small groups (arrowheads). The branch point of the fiber bundle (arrow) corresponds to the arrow in (A). Scale bar = 50 μ m. (Unpublished data; G. Rosado-Mattei and MWM, Institute of Neurobiology, University of Puerto Rico.)

their role in the transmission of sensory information. Faller *et al.* (2008) examined THli subepidermal sensory neurons in the cephalic sensory organs of several opisthobranchs and advanced a role for these cells in contact chemoreception or mechanoreception. Similar cells are abundant in the cephalic sensory organs of the pulmonates *Lymnaea stagnalis* and *Biomphalaria glabrata* (Wyeth and Croll, 2011; Vallejo *et al.*, 2014; Fig. 2A, B).

The potential sensory function of peripheral dopaminergic neurons was recently examined in the nudipleuran *Pleurobranchaea californica* (Brown *et al.*, 2018). Ciliated THli cells were highly concentrated in the oral veil and tentacle, sensory structures known to be important for food-seeking behavior (Fig. 2C). In freely behaving specimens, application of the D₂ antagonist sulpiride to the oral veil-tentacle complex produced a delay in the initiation of feeding responses. Sul-

piride also reduced spiking responses to tactile stimuli in the tentacle nerve. Together, these observations support a role of DA in the peripheral processing of food-related stimuli (Brown *et al.*, 2018).

Dopamine is also proposed to function as a proprioceptive signal in gastropod feeding systems. Early histological studies reported intense staining of catecholaminergic fibers in the esophageal nerve (Fekete *et al.*, 1984; Salimova *et al.*, 1987b; Rathousz and Kirk, 1988; Goldstein and Schwartz, 1989; Kabotyanski *et al.*, 1998). Double labeling (biocytin nerve tracing \times THli) revealed that some THli fibers in the esophageal nerve originate from DA neurons on the pharynx (Martínez-Rubio *et al.*, 2009; Fig. 2D). These histological observations prompted studies exploring the role of DA in mediating reinforcement in associative conditioning paradigms (see *Dopaminergic Reinforcement in Associative Learning*).

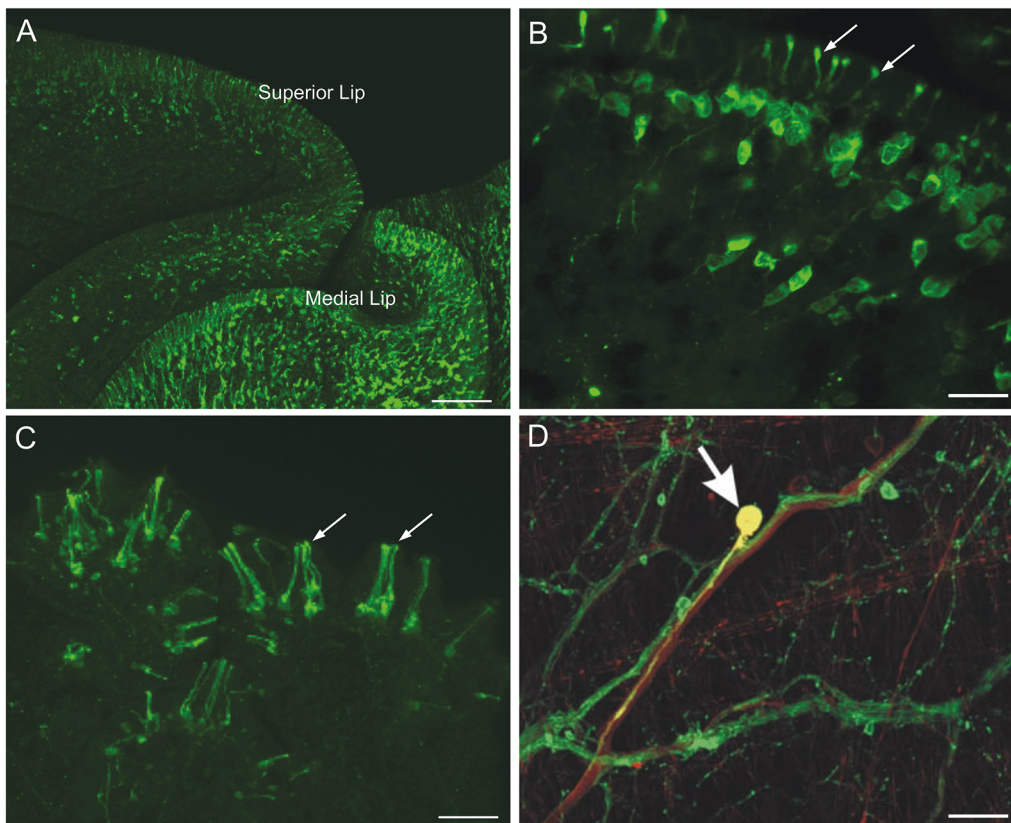


Figure 2. Dopamine as a sensory neurotransmitter in gastropods. (A) Low-magnification image showing abundant tyrosine hydroxylase-like immunoreactive (THli) innervation of the lips in *Biomphalaria glabrata*. Scale bar = 100 μ m. (B) Higher magnification of THli cells in the mantle integument of *Biomphalaria alexandrina*. A single process from each cell projects through the epithelium, terminating as a bulbous enlargement at the surface (arrows). Scale bar = 20 μ m. (A, B) Reprinted with permission from Vallejo *et al.*, 2014, *J. Comp. Neurol.* **522**: 2532–2552. (C) THli cells in the oral veil of *Pleurobranchaea californica*. Groups of cilia-like terminations (arrows) penetrate the epithelial surface. Scale bar = 20 μ m. Reprinted with permission from Brown *et al.*, 2018, *PLoS One* **13**: e0208891. (D) Esophageal nerve tracing (biocytin, red) and THli (green) on the surface of the pharynx of *Aplysia californica*. One double-labeled cell (yellow, arrow) in this merged image is a THli neuron that projects toward the central nervous system via the esophageal nerve. Scale bar = 50 μ m. Reprinted with permission from Martínez-Rubio *et al.*, 2009, *J. Comp. Neurol.* **514**: 329–342.

Giant Dopaminergic Neurons in Aquatic Pulmonates

Although most of the catecholaminergic neurons in gastropods are relatively small (10–40- μm soma diameter), a large (>200- μm) dopaminergic neuron (GDC [giant dopaminergic cell]) was detected by Marsden and Kerkut (1970) in the left pedal ganglion of *Planorbis corneus* (see also Pentreath *et al.*, 1974; Powell and Cottrell, 1974; Pentreath and Berry, 1975). Electrophysiological experiments demonstrated direct inhibitory and excitatory synaptic potentials from the GDC in neurons of the visceral and left parietal ganglion (Berry and Cottrell, 1973, 1975). These studies supported the role of DA as a multi-action neurotransmitter, capable of producing both excitatory and inhibitory actions on distinct synaptic targets upon release from a single neuron (Cottrell, 1967, 1977; Winlow and Benjamin, 1977).

The GDC of *P. corneus* was used to monitor DA storage and dynamics by using capillary electrophoresis with electrochemical detection and microelectrochemistry (reviewed by Anderson and Ewing, 1999). A low concentration of DA ($2.2 \pm 0.52 \mu\text{mol L}^{-1}$) was measured in the cytoplasm (Olefirowicz and Ewing, 1990). Amperometric measurements with a carbon fiber electrode detected current transients near the GDC soma in response to a high-potassium stimulation pulse (Chen *et al.*, 1995). Histograms constructed from the amplitudes of these current transients exhibited two peaks, which were proposed to represent somatic release of two distinct populations of DA-containing vesicles (Chen *et al.*, 1995).

A GDC is present in the left pedal ganglion of sinistral aquatic snails that possess a pneumostome breathing apparatus, including the genera *Helisoma* (*H. trivolvis*, McCaman *et al.*, 1979; Harris and Cottrell, 1995; *H. duryi*, Kiehn *et al.*, 2001) and *Biomphalaria* (*B. glabrata*, *B. alexandrina*, Vallejo *et al.*, 2014; Fig. 3). In the dextral pulmonate *Lymnaea stagnalis*, a corresponding GDC, designated RPeD1, was identified in the right pedal ganglion (Cottrell *et al.*, 1979; McCaman *et al.*, 1979; Winlow *et al.*, 1981; Elekes *et al.*, 1991; Werkman *et al.*, 1991). Syed and Winlow (1991a, b) showed that RPeD1 participates in the central pattern generator (CPG) circuit that controls respiration. In the isolated CNS, direct intracellular stimulation RPeD1 initiated coordinated rhythmic activity in the respiratory CPG (Syed *et al.*, 1990). In an *in vitro* reconstruction of the respiratory CPG, firing the RPeD1 neuron or pulsed application of DA were both capable of activating repetitive cycling (Syed *et al.*, 1990; Fig. 4A, B). These findings showed that dopaminergic signaling was sufficient for initiating or activating motor programs in the *Lymnaea* respiratory system.

Direct synaptic signals from the RPeD1 neuron of *Lymnaea* to its followers provided an opportunity to characterize the central dopaminergic synapses of gastropods. Magoski *et al.* (1995) showed that exogenous application of DA to identified follower neurons mimicked both excitatory and inhibitory synaptic actions of RPeD1. The D_2 antagonist sul-

piride blocked both inhibitory synaptic potentials evoked by RPeD1 and the inhibitory effects of exogenous DA ($\text{IC}_{50} = 1 \mu\text{mol L}^{-1}$; see Fig. 3C). Excitatory postsynaptic potentials (EPSPs) were blocked by picrotoxin (Magoski and Bulloch, 1999). Injection of postsynaptic neurons with GDP- β -S or incubation with pertussis toxin antagonized synaptic transmission, suggesting involvement of G-proteins in rapid (100–200-ms) dopaminergic signaling (Magoski *et al.*, 1995).

Feeding Motor Systems of Pulmonates

Involvement of DA in the regulation of gastropod feeding was initially demonstrated in the terrestrial slug *Limax maximus* (Wieland and Gelperin, 1983). High levels of DA were measured in the buccal and cerebral ganglion by using high-performance liquid chromatography with electrochemical detection (buccal: $19.4 \pm 2.4 \text{ pmol}$; cerebral: $124 \pm 33 \text{ pmol}$). No norepinephrine, epinephrine, or other metabolites of DA were detected. Application of exogenous DA ($>1 \times 10^{-6} \text{ mol L}^{-1}$) to the isolated cerebral-buccal system produced coordinated feeding motor programs that resembled programs elicited by stimulation of the chemosensory lips with apple juice. Moreover, feeding motor programs produced by lip stimulation were eliminated in the presence of the DA antagonist ergonovine.

In *Helisoma trivolvis*, high levels of ^3H -dopamine were synthesized from ^3H -tyrosine in the pedal, cerebral, and buccal ganglia (Trimble *et al.*, 1984). The Falck-Hillarp and glyoxylic acid protocols both labeled small (15–35- μm) cell bodies in the buccal ganglion, and bath application of DA (10^{-8} to $10^{-4} \text{ mol L}^{-1}$) to the isolated buccal ganglion initiated the patterned motor output characteristic of feeding (Trimble and Barker, 1984). In preparations that were producing spontaneous bouts of patterned motor output, addition of DA increased the impulses per burst and the burst duration of buccal motor neurons.

Stimulation of one labeled neuron in each buccal hemiganglion of *Helisoma* also initiated feeding motor patterns (Quinlan and Murphy, 1997). The motor programs produced by this cell, designated N1a, and those elicited by application of DA were both blocked by sulpiride. Because N1a was excited by feeding stimulants applied to the buccal cavity, and because programs could be attenuated when it was hyperpolarized, dopaminergic signaling from N1a was proposed to serve as a key determinant in the initiation of feeding behavior (Quinlan and Murphy, 1997).

In *Lymnaea stagnalis*, superfusion of DA to the isolated CNS also activated feeding motor programs (Kyriakides and McCrohan, 1989). In spontaneously active preparations, DA increased the frequency of motor programs. Dopamine also increased the firing rate of the cerebral giant cell, a higher-order serotonergic neuron that projects to the buccal ganglion (Kyriakides and McCrohan, 1989).

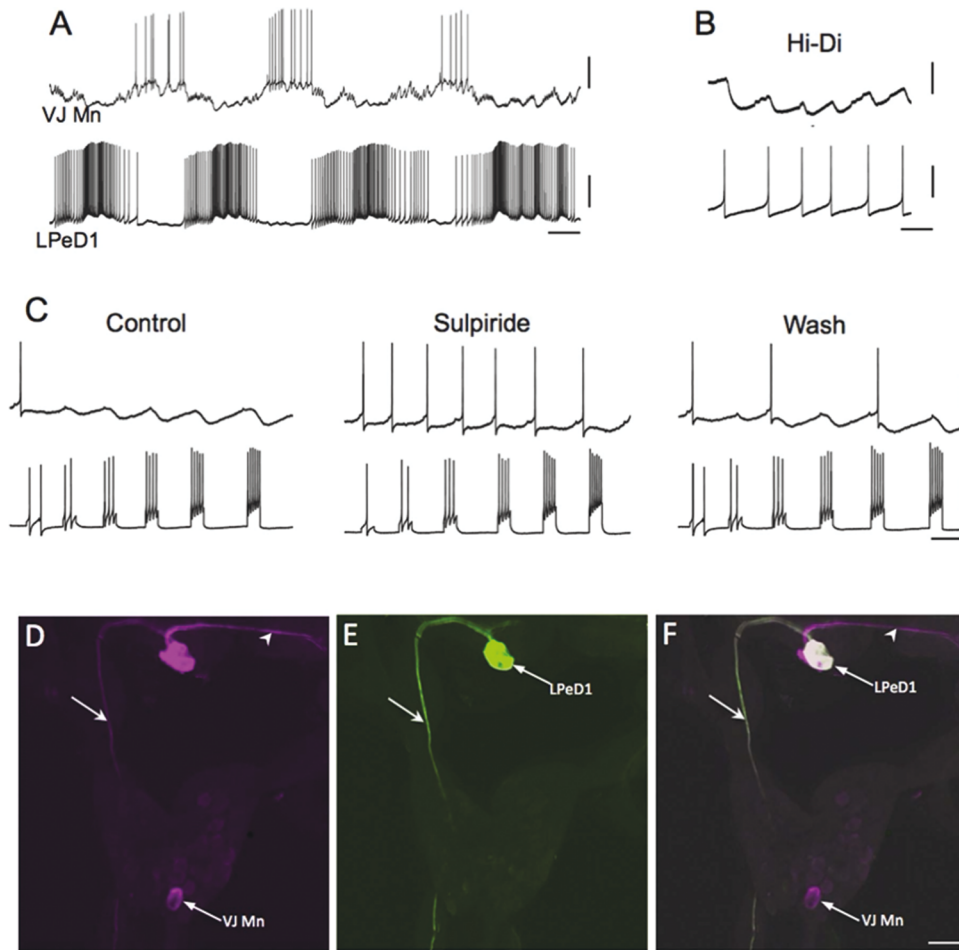


Figure 3. Giant dopaminergic pedal neuron of *Biomphalaria glabrata*. (A) Intracellular recording from LPeD1 (lower trace) of *B. glabrata*; isolated central nervous system in normal saline solution. The recording exhibits alternating phases of activity and quiescence. A putative cardio-respiratory motor neuron in the visceral ganglion (VJ Mn, upper trace) was observed to burst out of phase with LPeD1. Scale bars = 5 s; 20 mV for upper and lower records. (B) Changing the bathing medium to a raised divalent saline solution (Hi-Di) eliminated polysynaptic signaling, enabling resolution of direct one-to-one inhibitory postsynaptic potentials (IPSPs, upper record). Each IPSP occurred with a brief and constant latency following each LPeD1 impulse (lower record). Scale bars = 1 s; 5 mV, upper record; 20 mV, lower record. (C) Pharmacological evidence for direct dopaminergic signaling from LPeD1 to VJ Mn. Control indicates depolarizing current pulses passed into LPeD1, producing a sequentially greater number of impulses (lower record). The IPSPs produced in the VJ Mn became progressively larger as more impulses were stimulated. When the dopaminergic (D_2) antagonist sulpiride was added to the solution ($100 \mu\text{mol L}^{-1}$), the IPSPs were blocked. They returned after about a 15-min wash (right panel). Scale bars = 0.5 s; 20 mV for upper and lower records. (D–F) Morphological confirmation of LPeD1 and VJ Mn identity. (D) Neurobiotin was injected into LPeD1, a second neighboring cell in the pedal ganglion, and the VJ Mn. The three injected neurons were visualized with Avidin 546 (magenta pseudo-color). The axon of LPeD1 can be seen descending through the left pleural ganglion (arrow), while the neighboring cell projects to the contralateral pedal ganglion (arrowhead). (E) When the preparation was processed for tyrosine hydroxylase-like immunoreactivity and viewed with Avidin 488 (green), only the LPeD1 neuron and its descending axon (arrow) were labeled. (F) When the fill (D) and immunohistochemical (E) panels were overlaid, only the LPeD1 neuron and its descending axon (arrow) appear white (colocalization). The other injected cells, VJ Mn and the neighboring pedal neuron (arrowhead), appear magenta. Scale bar = $50 \mu\text{m}$, applies to (D–F). Reprinted from Vallejo *et al.*, 2014, *J. Comp. Neurol.* **522**: 2532–2552, with permission from John Wiley & Sons, Inc.

Collectively, studies on feeding networks of the pulmonates *Limax*, *Helisoma*, and *Lymnaea* demonstrated that DA can activate coordinated motor programs upon global application to complex CPG circuits. Such modulatory actions

tend to occur at concentrations (micromolar) that are lower than those reached within the synaptic cleft (millimolar) and that last as long as DA is present, that is, they do not desensitize (see also Matsumoto *et al.*, 1987; Kiss *et al.*, 2003;

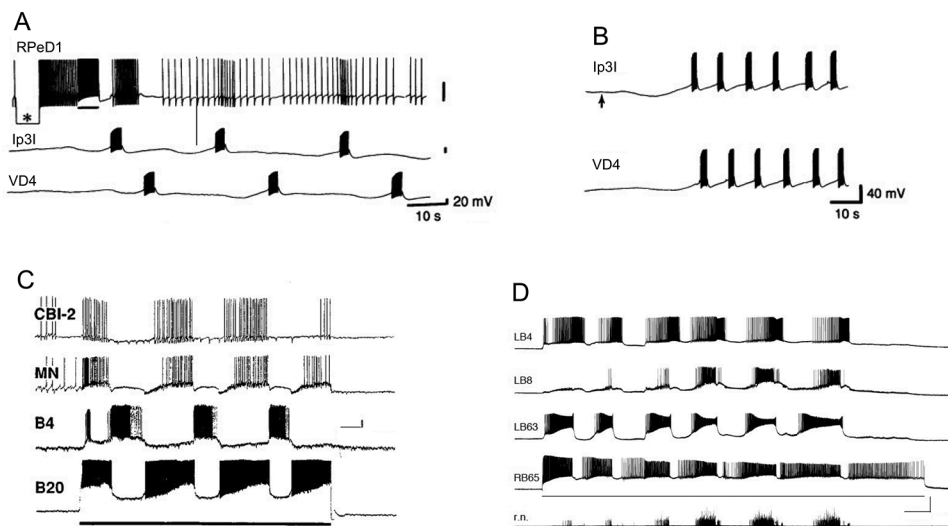


Figure 4. Dopamine (DA) activates central pattern generator (CPG) circuits of gastropods. (A) The dopaminergic RPeD1 interneuron of *Lymnaea stagnalis* was co-cultured with interneurons Ip3I and VD4 for 24 h, allowing the 3 cells to extend neurites and form synapses. Passing hyperpolarizing current into RPeD1 (asterisk) established that there was no electrical coupling between the cells. Passing depolarizing current that caused RPeD1 to fire (bar below upper recording) initiated repetitive expression of the respiratory CPG rhythm. Modified from Syed *et al.*, 1990, *Science* **250**: 282–285, used with permission. (B) Two non-dopaminergic interneurons that belong to the respiratory CPG, Ip3I and VD4, were co-cultured for four days, allowing synapses to form between them. Pulsed application of DA (1-s pulses at 0.3 Hz, beginning at upward arrow) from a fire-polished micropipette produced alternating bursts of impulses in the two interneurons. Modified from Syed *et al.*, 1990, *Science* **250**: 282–285, used with permission. (C) Stimulation of dopaminergic neuron B20 produces rhythmic motor patterns in the buccal ganglion of *Aplysia californica*. Depolarizing current (line below B20 recording) was passed from an intracellular microelectrode. The buccal motor program was monitored in the buccal interneuron B4, an unidentified motor neuron (MN) in the ventral cluster of the buccal ganglion, and a cerebral-buccal interneuron (CBI-2). Scale bars = 10 s, 10 mV. Reprinted with permission from Teyke *et al.*, 1993, *Brain Res.* **630**: 226–237. (D) Stimulation of dopaminergic neuron B65 produces rhythmic motor patterns in the buccal ganglion of *A. californica*. Depolarizing current (3.3 nA, line below B65 recording). B65 fired in phase with the protraction phase neuron LB63 and out of phase with the retraction phase interneuron LB4. Activity in the radula closer motor neuron LB8 and on the radula nerve (r.n.) increased in successive cycles of the motor program. Scale bars = 10 s, 40 mV, 100 μ V. Reprinted with permission from Kabotyanski *et al.*, 1998, *J. Neurophysiol.* **79**: 605–621.

Hernádi *et al.*, 2008). In common with the respiratory CPG circuit of pulmonates described above (see *Giant Dopaminergic Neurons in Aquatic Pulmonates*), individual dopaminergic neurons that are intrinsic to the feeding circuits can activate coordinated motor programs.

Multilevel Dopaminergic Control of a Multifunctional Central Pattern Generator

Aplysia feeding is a complex motivated behavior that can be elicited and modified *via* diverse sensory pathways (Kupfermann, 1974; Cropper *et al.*, 2017). The CPG network that controls *Aplysia* feeding exhibits multifunctionality, thus producing distinct behaviors *via* the activation or suppression of specific interneurons (Jing and Weiss, 2001; Kupfermann and Weiss, 2001). The presence of identified DA interneurons within the *Aplysia* feeding CPG provides opportunities to examine the contribution of dopaminergic synaptic signaling to the generation and selection of behavior by a multifunctional neural network (Figs. 4C, D, 5A).

Modifications of the paraformaldehyde and glutaraldehyde technique revealed five catecholaminergic neurons in the buccal ganglion of *Aplysia californica* (Rathouz and Kirk, 1988; Goldstein and Schwartz, 1989; Croll, 2001). Teyke *et al.* (1993) observed staining in a pair of small (20–30- μ m) bipolar buccal interneurons, designated B20, that could evoke coordinated buccal motor programs (BMPs) when stimulated (Fig. 4C). The B20 neurons were activated during programs produced by sensory input (pharyngeal stretch) and by higher-order cerebral-buccal order interneurons. They were proposed to act as intrinsic modulators of the buccal feeding CPG circuit (Teyke *et al.*, 1993).

In addition to evoking coordinated BMPs, B20 can specify the type of program elicited by higher-order interneurons (Jing and Weiss, 2001; Fig. 4A) or by peripheral nerve stimulation (Proekt *et al.*, 2004, 2007); B20 fires during the protraction phase of motor programs, thus providing strong excitatory signals to motor neurons that cause radula closure and, hence, egestive motor patterns (Fig. 5A₁, left). When the two B20 neurons were hyperpolarized and prevented from

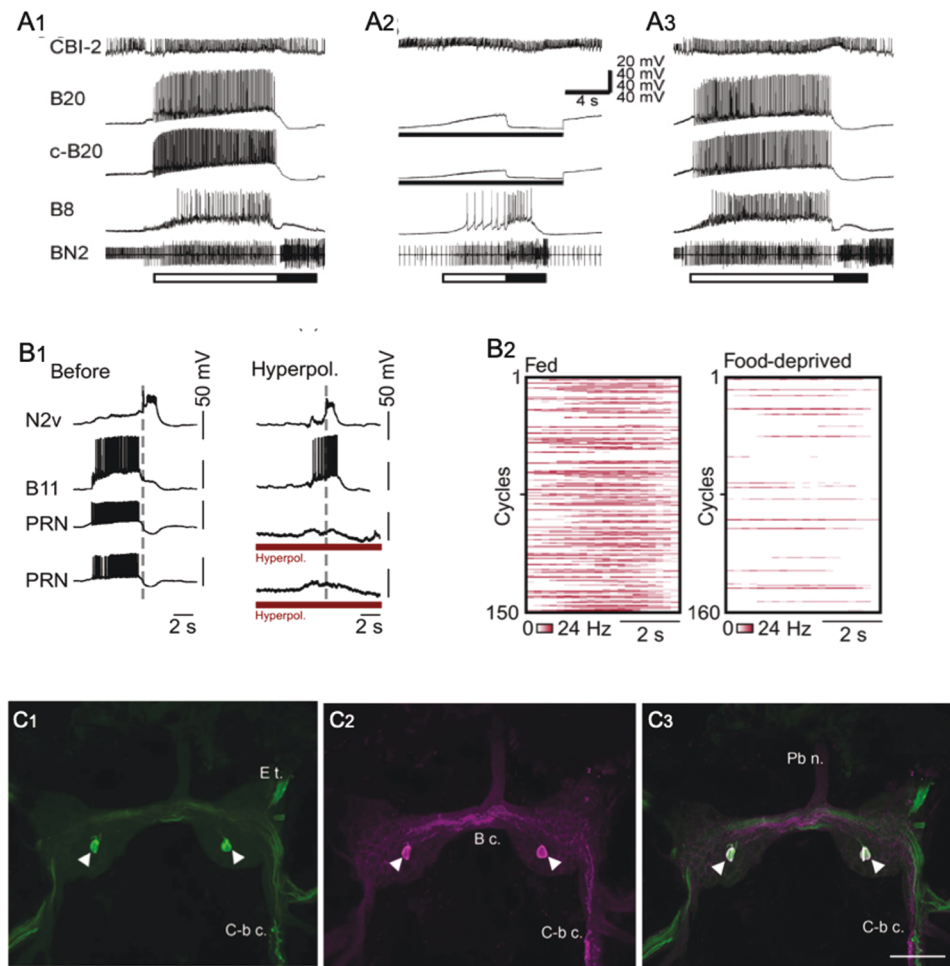


Figure 5. Motor program selection and stimulus valuation by identified gastropod interneurons. (A₁–A₃) Preventing firing of dopaminergic interneuron B20 converts egestive buccal motor patterns to ingestive programs in *Aplysia californica*. Programs were elicited by tonic firing of cerebral-buccal interneuron 2 (CBI-2, top record). The bar below the bottom record shows the protraction (open bar) and retraction (filled bar) phases of the motor programs, as determined from the extracellular recording of buccal nerve 2 (BN2). When no current was passed into the two B20 neurons (A₁ and A₃), they fired intensively during the protraction phase. The B8 radula closer motor neuron was also highly active during the protraction phase, indicative of egestive motor programs. When both B20 neurons were prevented from firing by passing intracellular current (A₂), the strongest B8 firing occurred during the retraction phase, characteristic of ingestive motor programs. Reprinted with permission from Jing and Weiss, 2001, *J. Neurosci.* **21**: 7349–7362. (B₁, B₂) The pattern-reversing neurons (PRNs) of *Lymnaea stagnalis* specify egestive motor programs and are active according to hunger state. (B₁) Preventing the PRNs of *Lymnaea* from participating in feeding motor programs converts them from their egestive form to their ingestive form. In a preparation dissected from a well-fed specimen (left panel), a tactile stimulus to the esophagus produced an egestive motor pattern, in which the motor neuron B11 fired during the protraction phase (left of the vertical dashed line; out of phase with the retraction interneuron N2V). When the two PRN neurons were hyperpolarized (Hyperpol.) by intracellular current injection (right panel, red bars below PRN recordings), the esophageal stimulus produced an ingestive motor program, evidenced by predominant B11 firing during the retraction phase (right of the vertical dashed line; in phase with the retraction interneuron N2V). (B₂) Heat plots of PRN firing rates during *in vitro* feeding cycles from fed ($n = 150$ cycles, 15 preparations) versus food-deprived (160 cycles, 16 preparations) specimens. Reprinted with permission from Crossley *et al.*, 2018, *Sci. Adv.* **4**: eaau9180. (C₁–C₃) Colocalization of tyrosine hydroxylase-like immunoreactivity and gamma-aminobutyric acid-like reactivity in presumptive PRN of *Lymnaea stagnalis*. (C₁) As reported by Crossley *et al.* (2018), tyrosine hydroxylase-like immunoreactivity was detected in a single cell on the ventral surface of the buccal ganglion of *Lymnaea*. (C₂) Gamma-aminobutyric acid-like immunoreactivity was present in the same cell (magenta pseudo-color). (C₃) Merge of (C₁) and (C₂) confirms colocalization of tyrosine hydroxylase-like immunoreactivity and gamma-aminobutyric acid-like immunoreactivity (cell appears white). B c., buccal commissure; C-b c., cerebral-buccal connective; E t., esophageal trunk; Pb n., parabuccal nerve. Scale bar = 100 μ m applies to (C₁–C₃). Reprinted with permission from Vaasjo *et al.*, 2018, *J. Comp. Neurol.* **526**: 1790–1805.

firing *via* intracellular current injection, motor programs exhibited their ingestive configuration (Fig. 5A₂; Jing and Weiss, 2001). Rapid dopaminergic signaling was shown to be responsible for such motor program specification, because EPSPs from B20 to decisive buccal motor neurons were occluded by exogenous DA and blocked by sulpiride (Díaz-Ríos *et al.*, 2002).

Recently, a bilateral pair of dopaminergic cells, termed pattern reversing neurons (PRNs), was identified in the buccal ganglion of *Lymnaea stagnalis* (Crossley *et al.*, 2018). Firing an individual PRN produced egestive motor patterns, that is, programs that would cause the snail to reject a potential food stimulus. The PRN was highly active during spontaneous egestive motor programs recorded from nervous systems dissected from satiated specimens (Fig. 5B₂, left), and PRN activity was low in ingestive feeding cycles produced by ganglia dissected from food-deprived specimens (Fig. 5B₂, right). As shown for B20 in *Aplysia*, when the two PRNs were prevented from firing, egestive programs were converted to their ingestive form (Fig. 5B₁). These observations led to the proposal that dopaminergic signaling defines the perceived value of a stimulus and biases the feeding motor circuit to reflect the motivational state of the snail (Crossley *et al.*, 2018). In view of their morphology, neurotransmitter phenotype, and ability to bias the buccal network toward its egestive mode, the PRNs of *Lymnaea* (Crossley *et al.*, 2018) are likely to be homologous to the B20 neurons of *A. californica* (see also Murphy, 2001; Vaasjo *et al.*, 2018).

A second pair of dopaminergic interneurons, termed B65, was localized to the lateral region of the caudal surface of the *Aplysia* buccal ganglion (Kabotyanski *et al.*, 1998). In contrast to B20, but like neuron N1a of *Helisoma* (see Murphy, 2001), B65 is a monopolar neuron that does not project to the cerebral ganglion. Each B65 produces excitatory and inhibitory postsynaptic potentials in both ipsilateral and contralateral buccal motor neurons and can initiate repeated bouts of BMPs (Fig. 4D). Dopaminergic signaling by B65 was proposed to contribute to the specification of motor patterns by the polymorphic buccal CPG (Kabotyanski *et al.*, 1998, 2000). This hypothesis was supported by experiments in which both B65 neurons were prevented from firing during BMPs produced by stimulation of the esophageal nerve (Due *et al.*, 2004; see also Dacks and Weiss, 2013). Hyperpolarizing both B65 neurons, or application of the DA antagonist sulpiride, resulted in motor programs that were biased toward their ingestive conformation.

Thus, while firing dopaminergic interneurons B20 and B65 in *Aplysia*, or PRN in *Lymnaea*, can elicit coordinated buccal programs, their activity is not required for program expression. When motor patterns are generated *via* other pathways, dopaminergic signaling can qualitatively specify the output from the multifunctional feeding CPG network. Interestingly, the excitatory B65-B20-motor neuron pathway constitutes a disynaptic dopaminergic feedforward network motif that promotes a specific response, that is, egestive movements (Jing

and Weiss, 2001; Díaz-Ríos and Miller, 2005, 2006; Proekt *et al.*, 2007).

While the specification of egestive motor programs by interneurons B20 and B65 is largely achieved *via* rapid dopaminergic synaptic signals, DA can also exert modulatory actions that modify the intrinsic properties of motor neurons in the feeding system of *Aplysia*. Application of DA or firing B65 converts sporadic and asynchronous burst activity into rhythmic and synchronized bursting in the bilaterally paired pharyngeal B67 motor neurons (Serrano and Miller, 2006). The increased synchrony was proposed to reflect dopaminergic enhancement of an intrinsic burst-forming “driver potential” and increased electrical coupling between the B67 pair (Serrano and Miller, 2006; see also Martínez-Rubio *et al.*, 2010). Because the capacity for a neuromodulator to elicit burst activity from otherwise quiescent neurons was previously designated “conditional bursting” (Marder and Eisen, 1984; Harris-Warrick and Marder, 1991), the rhythmicity and synchrony produced by DA in the paired B67 cells were referred to as “conditional rhythmicity” and “conditional synchrony,” respectively (Serrano and Miller, 2006; Nargeot *et al.*, 2009).

Finally, the feeding motor circuits of *Aplysia* are also influenced by dopaminergic signaling originating from extrinsic sources, including higher-order neurons projecting from the cerebral ganglion (Rosen *et al.*, 1991). A bilateral pair of cerebral-buccal interneurons, termed CBI-1, exhibits catecholamine histofluorescence when treated with the paraformaldehyde-glutaraldehyde technique. Firing this higher-order neuron elicits a single cycle of BMP activity that incorporates dopaminergic buccal interneuron B20 (Rosen *et al.*, 1991). In semi-intact preparations of *Aplysia kurodai*, a pair of dopaminergic cerebral neurons (CBM1) thought to be homologous to CBI-1 of *A. californica* biases the feeding motor circuitry toward rejection of nonpreferred foods (Narusuye and Naga-hama, 2002). As noted previously for B65-B20-motor neuron signaling intrinsic to the buccal CPG, the extrinsic CBI-1-B20-motor neuron pathway also utilizes a feedforward dopaminergic configuration that promotes rejection of unwanted material.

Dopamine Colocalization with Gamma-Aminobutyric Acid

Tyrosine hydroxylase-like immunoreactivity and CA histofluorescence were reported to be colocalized with gamma-aminobutyric acid (GABA)-like immunoreactivity in five neurons in the buccal ganglion of *Aplysia californica* (Díaz-Ríos *et al.*, 2002). DA-GABA colocalization was not detected elsewhere in the central or peripheral nervous systems. Physiological experiments showed that four of the DA-GABA cells correspond to the paired B20 and paired B65 neurons (see *Multilevel Dopaminergic Control of a Multifunctional Central Pattern Generator*, above). The fifth

DA-GABA neuron is an unpaired cell on the caudal surface of the left buccal ganglion that has not yet been identified. Rapid synaptic signaling from both B20 and B65 to identified follower motor neurons was occluded by DA and blocked by sulpiride, supporting their dopaminergic phenotype (Due *et al.*, 2004; Díaz-Ríos and Miller, 2005).

Gamma-aminobutyric acid antagonists did not block signals from B20 or B65, but GABA and the GABA_B agonist baclofen did increase the amplitude of their dopaminergic EPSPs (Díaz-Ríos and Miller, 2005). When B20 was fired repetitively to mimic its activity during motor programs, GABA and baclofen also enhanced two forms of synaptic plasticity: facilitation and summation (Díaz-Ríos and Miller, 2006). In view of the DA-GABA colocalization in B20, this modulation was designated “homosynaptic modulatory metaplasticity” (Díaz-Ríos and Miller, 2006). The GABAergic modulation of dopaminergic signaling from B20 was shown to be mediated *via* postsynaptic activation of G-protein-dependent protein kinase C (Svensson *et al.*, 2014).

Recently, colocalization of TH-like and GABA-like immunoreactivity was observed in five neurons in the buccal ganglia of the pulmonates *Biomphalaria glabrata*, *Helisoma trivolvis*, and *Lymnaea stagnalis* (Fig. 5C₁–C₃; Vaasjo *et al.*, 2018). These observations support the hypothesis that the CPG for gastropod feeding exhibits a common plan across the panpulmonate and euopisthobranch clades (Murphy, 2001; Wentzell *et al.*, 2009). They also support the proposal that the PRN of *Lymnaea* corresponds to B20 in *Aplysia californica* (see *Multi-level Dopaminergic Control of a Multifunctional Central Pattern Generator*, above).

Dopaminergic Reinforcement in Associative Learning

Accumulating evidence supports a role for DA in both classical and operant conditioning of gastropods (see Baxter and Byrne, 2006; Kemenes *et al.*, 2010; Nargeot and Simmers, 2010, 2012; Mozzachiodi *et al.*, 2013; Aonuma *et al.*, 2016; Nargeot and Bédécarrats, 2017). Pavlovian appetitive conditioning was demonstrated in the feeding system of *Aplysia californica* by pairing a neutral tactile stimulus (conditioned stimulus) with food presentation (unconditioned stimulus) (Colwill *et al.*, 1997; Lechner *et al.*, 2000a). Appetitive operant conditioning was shown by stimulating a branch of the esophageal nerve (En₂, see below; Brembs *et al.*, 2002) or presenting a food reward (Nargeot *et al.*, 2007) contingent upon expression of consummatory biting behavior. Neurophysiological sequelae of both forms of conditioning could be detected in nervous systems dissected from trained specimens (Lechner *et al.*, 2000b; Brembs *et al.*, 2002). Moreover, *in vitro* analogs for both paradigms exhibit modifications of fictive feeding motor patterns that recapitulate *in vivo* conditioning (classical conditioning: Mozzachiodi *et al.*, 2003; Reyes *et al.*, 2005; operant conditioning: Nargeot *et al.*, 1997, 1999a).

The anterior branch of the esophageal nerve (En₂) was identified as a pathway that was necessary and sufficient for transmission of the unconditioned stimulus in the Pavlovian paradigm and reinforcement in operant conditioning (Nargeot *et al.*, 1997; Lechner *et al.*, 2000a; Brembs *et al.*, 2002; Mozzachiodi *et al.*, 2003; see also Schwarz and Susswein, 1986). As described above, En₂ is rich in catecholaminergic fibers, some of which originate from TH_{li} cells on the wall of the pharynx (Martinez-Rubio *et al.*, 2009; see *Dopamine as a Sensory Neurotransmitter*; Fig. 2D).

Low concentrations (1 nmol L⁻¹) of the DA antagonist methylergonovine blocked conditioned enhancement of ingestive motor programs produced by stimulation of the esophageal nerve in analogs of operant and classical conditioning (Nargeot *et al.*, 1999c; Reyes *et al.*, 2005). Thus, investigation focused on a specific identified neuron, B51, that acts as a pivotal decision-making element for the specification of ingestive BMPs (Nargeot *et al.*, 1999a, b). Brembs *et al.* (2002) tested a single-cell analog for operant conditioning by using pulsed application of DA onto B51 isolated from the buccal ganglion of naive specimens. When DA application was contingent upon expression of plateau potentials by B51, subsequent tests revealed a significant increase in the input resistance and a decrease in burst threshold (Brembs *et al.*, 2002). These biophysical changes were shown to reflect activation of second messenger pathways acting through protein kinase A and protein kinase C *via* a D₁-like DA receptor (Barbas *et al.*, 2006; Lorenzetti *et al.*, 2008; Mozzachiodi *et al.*, 2008).

Using a modified version of the operant conditioning paradigm in behaving *Aplysia*, Nargeot and coworkers (2007, 2009) observed a significant increase in the frequency and rhythmicity of biting. Several changes in the buccal network, including regularization of the burst discharge and increased electrical coupling of pattern-initiating cells, were detected after dissection from contingent-reward trained specimens (Nargeot *et al.*, 2009; Sieling *et al.*, 2014). These modifications were replicated in an *in vitro* paradigm that used stimulation of the DA-rich En₂ as a reinforcing stimulus (Bédécarrats *et al.*, 2013). When the D₁ receptor antagonist flupenthixol was present during training, rhythmic programs were not observed in trained preparations, and physiological changes did not occur in the pattern-initiating cells. The regularly repeating, compulsive-like expression of feeding behavior was proposed to require dopaminergic contingent reward signals from En₂ (Bédécarrats *et al.*, 2013).

Discussion

Evolution of dopamine as a multifunctional neurotransmitter

The findings reviewed here support the role of DA as a multifunctional neurotransmitter in gastropods and suggest a hypothetical progression by which DA acquired its diverse

roles. This sequence can be readily examined in the networks that control feeding-related behaviors (Fig. 6). At each stage of this progression, the function of DA neurons is proposed to favor their recruitment to their subsequent role, as the circuits gained increasing complexity and adaptive control. Common functions of DA across phylogeny imply the ancient origin of this sequence, possibly preceding the divergence of deuterostomes and protostomes (see Hills, 2006; Barron *et al.*, 2010). There is presently some debate regarding the body plan and nervous system organization of the last common bilaterian ancestor (see Moroz, 2009; Hirth, 2010; Northcutt, 2012; Strausfeld and Hirth, 2013). However, paleontological evidence suggests that the oldest well-documented bilaterian, *Kimberella* (555 million years ago [Mya]), had a slug-like form and fed by scratching the microbial surface on which it lived (Fedonkin and Waggoner, 1997). Such an organism would, in all likelihood, possess a nervous system that could sense potential nutrients and activate a scraping apparatus.

Sensation. The presence of subepithelial dopaminergic neurons lining the cephalic sensory organs of several gastropod groups (Fig. 2A–C) indicates that DA signaling participates in the transduction of stimuli associated with foraging or food-seeking behavior (Fig. 6A: Sensation). To date, the modality of the peripheral dopaminergic neurons remains unresolved, but their projections through the body wall suggest either a tactile or a chemosensory function (see Croll, 2001; Faller *et al.*, 2008; Wyeth and Croll, 2011; Vallejo *et al.*, 2014). The participation of sensory DA signaling in food-seeking behavior is also supported by pharmacological observations in *Pleurobranchaea* (Brown *et al.*, 2018).

Sensory signaling in foraging behaviors appears to be an ancient function of DA, at least predating divergence of the Ecdysozoa and Lophotrochozoa superphyla (581–531 Mya; Hedges and Kumar, 2009). In the simpler nervous system of the nematode *Caenorhabditis elegans*, consisting of only 302 neurons, all known dopaminergic neurons (8 in the hermaphroditic form and 14 in the male form) have a sensory function (Chase and Koelle, 2007). Stimulation of dopaminergic mechanosensory neurons by bacterial food reduces crawling speed and increases turning behavior (Sawin *et al.*, 2000; Hills *et al.*, 2004; Rivard *et al.*, 2010). Both of these changes in reward-seeking behavior promote an area-restricted search, thus increasing the likelihood that *C. elegans* will remain in a location where food is encountered (Hills, 2006).

Activation. When repetitive stereotyped movements came under the control of CPG circuits, dopaminergic sensory neurons may have been recruited to regulate their activation (Fig. 6B: Activation). In the gastropods, a limited number of neurons could have migrated to the CNS and become integrated into certain CPGs (see McAllister *et al.*, 1983; Gillette and Brown, 2015). In the aquatic pulmonates, the respiratory system CPG contains a dopaminergic neuron that is capable of activating the quiescent central circuit (Figs. 3, 4A, B). In the snails that have been studied, *Helisoma trivolvis* and *Lym-*

naea stagnalis, the GDC participates in each cycle of the respiratory motor pattern and acts as an intrinsic constituent of the respiratory CPG (see Fig. 4A, B).

Activation of the *Aplysia* feeding motor system can also be achieved by dopaminergic signaling from a neuron that is extrinsic to the feeding CPG itself (CBI-1 in *Aplysia californica* and CBM1 in *Aplysia kurodai*). In contrast to the giant neurons in the pulmonate respiratory CPGs, the cerebral-buccal interneurons typically serve a command-like function and are not *sensu stricto* participants in each cycle of the feeding motor pattern. Such extrinsic activation of motor systems by DA occurs in multiple taxa, including the cardiac and stomatogastric CPGs of crustaceans (Anderson and Barker, 1981; Miller *et al.*, 1984; Fort *et al.*, 2004), the crawling CPG of the medicinal leech (Puhl and Mesce, 2008), and the spinal locomotor CPGs of fish and mammals (Svennson *et al.*, 2003; Barrière *et al.*, 2004; Sharples *et al.*, 2014). Recently, two-photon calcium imaging and optogenetics were used to demonstrate that dopaminergic nigrostriatal projections signal the initiation of locomotion bouts in mice (Howe and Dombeck, 2016; see also Jin and Costa, 2010).

Selection. When CPGs gained a level of complexity that supported multifunctionality (see Getting, 1989; Briggman and Kristan, 2008), the ability of dopaminergic neurons to activate motor systems could have facilitated their implementation for the specification of motor programs (Fig. 6C: Selection). This function is illustrated by the B20 and B65 interneurons in the buccal feeding network of *Aplysia* and by the PRN of *Lymnaea*. Activity of these dopaminergic neurons causes the buccal circuit to select one motor pattern, egestion, over another, ingestion (Fig. 5A, B). Interestingly, B20, B65, and the PRN all possess the ability to activate BMPs when stimulated (Kabotyanski *et al.*, 1998; Jing and Weiss, 2001; Crossley *et al.*, 2018). However, all are selectively recruited by stimuli that generate one class of motor program, egestion, from the multifunctional feeding circuit. When their participation in motor program generation is prevented, the circuit produces ingestive patterns (Fig. 5A, B). Thus, dopaminergic synaptic signaling from B20, B65 of *Aplysia*, and the PRN of *Lymnaea* specifies or selects the performance of egestive programs (Jing and Weiss, 2001; Due *et al.*, 2004; Crossley *et al.*, 2018).

In vertebrates, resolution of the “selection problem,” that is, execution of a specific behavior while inhibiting competing actions, is commonly attributed to the basal ganglia (Graybiel, 1995; Mink, 1996; Redgrave *et al.*, 1999). Participation of nigrostriatal dopaminergic neurons in action selection was suggested by early pharmacological studies (Cools, 1980). Recently, fast-scan cyclic voltammetry was used to measure sub-second changes in DA levels in the dorsal striatum of mice that were trained to select between two alternative actions. Higher DA levels and higher firing rates of nigrostriatal DA neurons were both specifically associated with behavioral choice (Howard *et al.*, 2017).

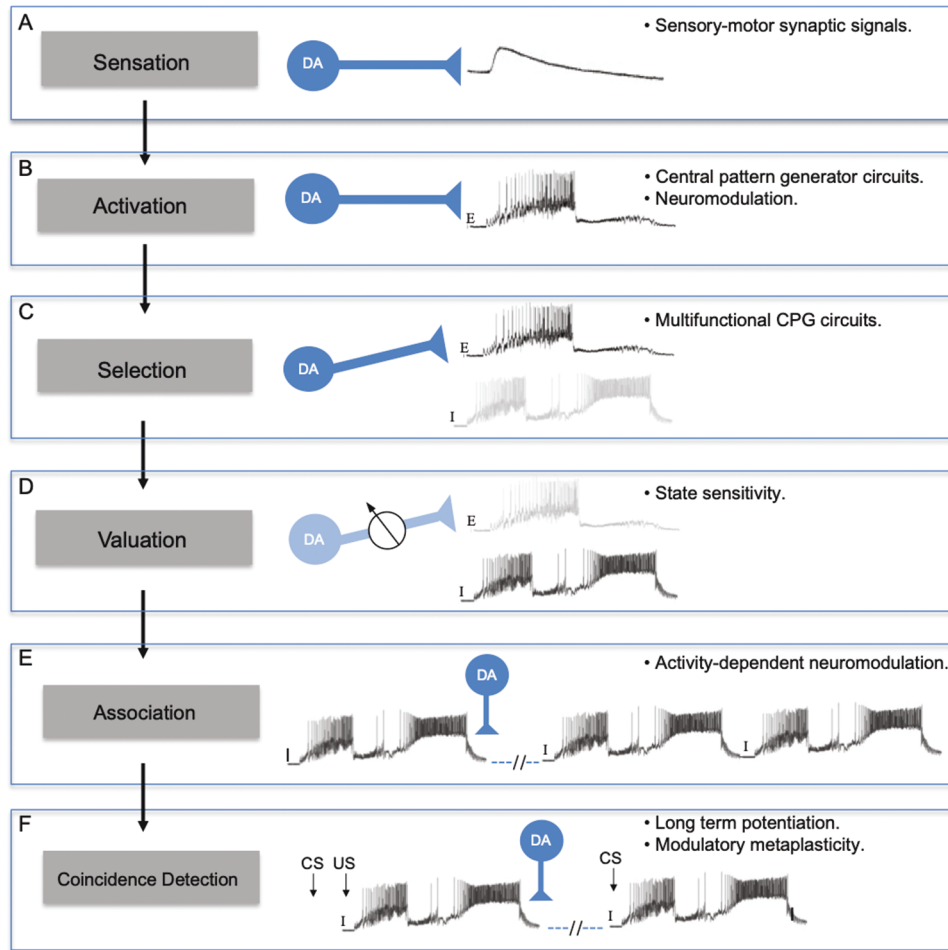


Figure 6. Sequential acquisition of dopamine (DA) functions in nervous systems. The proposed sequence is shown on the left (shaded boxes), using the feeding system of *Aplysia* as a prototype. Mechanisms or levels of nervous complexity that enabled DA to assimilate each function are shown at the right. According to this hypothesis: (A) Initially, DA-mediated sensory-motor synaptic signals could influence food-searching networks. (B) With the advent of central pattern generator (CPG) circuits, the role of DA as a sensory neurotransmitter favored its utilization as an activator of motor programs (E, egestive motor program). (C) With the elaboration of more complex multifunctional CPG circuits, the ability of DA to activate motor programs facilitated its implementation in the specification of one pattern *versus* another. Here, DA is shown selecting an egestive program (E, dark shading) from a network that can also produce ingestive (I, light shading) programs. (D) The ability of DA neurons to select a specific program from a multifunctional CPG led to their utility for factoring the value of a stimulus into such decisions. Here, state sensitivity causes dopaminergic signaling to be down-regulated (potentiometer, lighter blue shading) as the hunger level of the organism increased, decreasing activation of egestive (E) motor programs (lighter shading) and increasing the tendency toward ingestive (I) programs (dark shading). (E) The ability of DA to activate motor networks *via* modulatory second messenger cascades facilitated its deployment as a phasic reinforcing signal. Here, a DA pulse originating from pharyngeal sensory neurons is shown following a spontaneous ingestive motor pattern (I). Through activity-dependent modulation of rhythm- and burst-generating currents in key interneurons, the dopaminergic reinforcing signal causes the feeding CPG to produce repetitive ingestive programs. (F) The ability of dopaminergic sensory neurons to inform the feeding CPG about the consequences of its activity also led to their participation in stimulus coincidence detection. Here, modulatory DA signals enable a conditioned stimulus (CS) to evoke a specific behavior (ingestive motor pattern shown) following pairing with an unconditioned stimulus (US). Strengthening of synaptic input from the CS pathway to the feeding CPG is proposed to reflect enhancement of an intrinsic plasticity, such as long-term potentiation. In this paradigm, the actions of DA constitute a form of modulatory metaplasticity.

Valuation. The capacity for dopaminergic neurons to specify behavior produced by multifunctional motor networks could have favored their implementation by systems that factor an assessment of stimulus value or utility into such selection (Fig. 6D: Valuation). Such valuation could be implemented by adjusting the strength of DA signaling according to the motivational state of the organism (denoted by the potentiometer in Fig. 6D).

Dopaminergic signaling by the PRNs of *L. stagnalis* causes the feeding circuit to produce egestive motor programs in satiated specimens in response to tactile or chemical stimuli (Crossley *et al.*, 2018). The PRNs are not active in food-deprived snails, which produce ingestive behaviors in response to the same stimuli. It was proposed that these higher-order interneurons encode hunger state (satiated vs. hungry) and select corresponding motor patterns (egestive vs. ingestive) from the multifunctional feeding circuit (Crossley *et al.*, 2018). Suppression of PRN activity thus enables hungry snails to increase their valuation of food stimuli.

A similar neural architecture is present in *Drosophila*, where six dopaminergic interneurons in the mushroom bodies prevent expression of conditioned feeding in satiated flies (Krashes *et al.*, 2009). Inhibition of these interneurons, termed MB-MP cells, by an ortholog of the mammalian neuropeptide Y (neuropeptide F), mimics food deprivation and promotes memory performance in satiated flies. Interestingly, the *Aplysia* ortholog of neuropeptide Y was shown to mediate satiety signals from the esophagus, at least in part by increasing the activity of the DA-GABA interneuron B20 (Jing *et al.*, 2007), proposed here to correspond to the PRN of *Lymnaea*.

In vertebrates, motivational state can assign value to sensory stimuli by modulating or filtering afferent signaling. Dopamine is a major neurotransmitter in the olfactory bulb of mice, where it is colocalized with GABA in juxtaglomerular cells that have extensive interglomerular projections (Kosaka *et al.*, 1985; Kosaka and Kosaka, 2008; Kiyokage *et al.*, 2010). In feeding systems, signaling in the olfactory bulb is modified by nutritional status (Aimé *et al.*, 2007; Prud'homme *et al.*, 2009). The extensive dopaminergic network in the cephalic sensory organs of gastropods has been likened to vertebrate juxtaglomerular cells, and it has been proposed that they could participate in the peripheral computation of stimulus value reflecting hunger or satiety (Gillette and Brown, 2015; Brown *et al.*, 2018).

Association. The ability to identify a temporal association between internal or external events is required for animals to form adaptive predictions (Pavlov, 1927; Skinner, 1938; Gallistel, 1990). To date, stimulation of the esophageal nerve has been used as the unconditioned stimulus for *in vitro* analogs of classical conditioning and as the reinforcing stimulus for two forms of operant conditioning in the *Aplysia* feeding system (Nargeot *et al.*, 1999a, b; Mozzachiodi *et al.*, 2003; Brembs *et al.*, 2002, 2004; Bédécarrats *et al.*, 2013). In all cases, it has been proposed that associations result from

the release of DA within the feeding CPG (Brembs *et al.*, 2002; Reyes *et al.*, 2005; Bédécarrats *et al.*, 2013). This hypothesis was supported by the demonstration of dopaminergic afferent neurons on the wall of the pharynx (Fig. 1D; Martínez-Rubio *et al.*, 2009). Such cells could provide rapid preabsorptive feedback to the buccal CPG concerning the consequences of feeding movements.

In some CPGs, slow currents in key interneurons can produce spontaneous behavior that is not elicited by a specific stimulus (see Nargeot and Simmers, 2012; Hawkins and Byrne, 2015). The ability of dopaminergic neurons to activate and select motor programs based on an assessment of value (Fig. 6A–D) could have favored the participation of DA in providing proprioceptive feedback to feeding CPGs (Fig. 6E: Association). For example, if a food-searching bite motor program was followed by a DA pulse that signified successful ingestion, the production of subsequent biting programs could be increased. As discussed above (*Activation*), tonic application of DA can initiate repetitive rhythmic motor activity in gastropod CPGs (*e.g.*, Fig. 4B; see also Wieland and Gelperin, 1983; Trimble and Barker, 1984; Serrano and Miller, 2006). Its implementation as a phasic reinforcing signal that can increase the occurrence of an operant is likely to reflect similar mechanistic actions, that is, modulation of rhythm- and burst-generating currents in key CPG elements (Nargeot *et al.*, 2009; Nargeot and Simmers, 2012). The ability of such phasic-reinforcing DA signals to associate the occurrence of a motor program with its consequences could reflect long-lasting, activity-dependent modulation of these currents.

Coincidence detection. The ability of dopaminergic neurons to influence feeding CPGs based on the consequences of their activity could have set the stage for their use in detecting temporal contiguity between a sensory stimulus and its consequences. In this scenario, a neutral stimulus that precedes successful passage of food through the pharynx would take on a subsequent predictive function (Fig. 6F: Coincidence detection). Although both instrumental and Pavlovian conditioning involve modulatory actions of DA originating from the esophageal nerve, the mechanisms for establishing associations differ for the two types of learning. While operant conditioning affects the intrinsic rhythm- and burst-generating currents in decision-making neurons, classical conditioning tends to reflect regulation of synaptic signals that reach those neurons through sensory pathways (Lechner *et al.*, 2000b; Mozzachiodi *et al.*, 2003, 2013; Lorenzetti *et al.*, 2005, 2011; Mozzachiodi and Byrne, 2008, 2010). Such modification of synaptic signals could be achieved *via* dopaminergic enhancement of an intrinsic coincidence detection mechanism, such as Hebbian long-term potentiation, in the sensory input to the feeding CPG.

In vertebrate nervous systems, midbrain dopaminergic neurons involved in appetitive conditioning are thought to receive sensory information, for example, taste or odor, that conveys the potential utility of a food stimulant (see Glimcher, 2011).

Table 1*Anatomic substrates of dopamine functions in gastropod and mammalian nervous systems*

Function	Gastropod nervous system	Mammalian nervous system
Sensation	Cephalic sensory organs (Wyeth and Croll, 2011, Faller <i>et al.</i> , 2008; Brown <i>et al.</i> , 2018)	Olfactory bulb (Kosaka <i>et al.</i> , 1985; Kosaka and Kosaka, 2008; Kiyokage <i>et al.</i> , 2010)
Activation	Cerebral-buccal command-like interneurons (Rosen <i>et al.</i> , 1991; Narusuye and Nagahama, 2002)	Nigrostriatal projections (Howe and Dombeck, 2016; see also Jin and Costa, 2010)
Selection	<i>Aplysia</i> buccal interneurons (B20 and B65) (Teyke <i>et al.</i> , 1993; Kabotyanski <i>et al.</i> , 1998; Jing and Weiss, 2001)	Nigrostriatal projections (Graybiel, 1995; Mink, 1996; Redgrave <i>et al.</i> , 1999; Howard <i>et al.</i> , 2017)
Valuation	<i>Aplysia</i> B20; <i>Lymnaea</i> PRN (Jing <i>et al.</i> , 2007; Crossley <i>et al.</i> , 2018)	VTA projections to ventral striatum (Kroemer <i>et al.</i> , 2016)
Association	Pharyngeal DA afferents (Martínez-Rubio <i>et al.</i> , 2009; Bédécarrats <i>et al.</i> , 2013)	VTA-striatal projections (Graybiel, 2005, 2008)
Coincidence detection	Pharyngeal DA afferents (Brembs <i>et al.</i> , 2002; Reyes <i>et al.</i> , 2005; Martínez-Rubio <i>et al.</i> , 2009)	VTA-striatal and cortical projections (Levine <i>et al.</i> , 1996; Williams and Goldman-Rakic, 1998; Schultz, 2010)

Selected references are shown for each function. DA, dopamine; VTA, ventral tegmental area.

Present models posit that these DA neurons encode a reward prediction error that uses such sensory information, or a proxy cue, to calculate whether the expectation of future reward requires revision (Montague *et al.*, 1996; Schultz *et al.*, 1997). Midbrain DA neurons project to motor control circuits of the basal ganglia and frontal cortex, where DA release reflects the reward prediction error magnitude (Williams and Goldman-Rakic, 1998; Björklund and Dunnett, 2007). In a leading mechanism for associative conditioning, DA modulation can produce a pairing-specific strengthening of sensorimotor pathways by enhancing long-term potentiation of synaptic connections (Levine *et al.*, 1996; Pawlak and Kerr, 2008; Lutz and Castillo, 2020). Thus, DA may make parallel contributions to Pavlovian conditioning in the gastropod and vertebrate nervous systems, that is, modulation of long-lasting, coincidence-detecting synaptic plasticity.

Future Directions and Perspective

Emerging research should continue to reveal how DA acquired and executes its various functions in gastropods. Promising areas of investigation include (1) use of voltage-sensitive dyes to explore global effects of DA on neural circuits (Neveu, 2017); (2) omics data that will lead to the identification, characterization, and localization of DA receptors involved in motor control and learning (Barbas *et al.*, 2006; Tamvacakis *et al.*, 2015; Mansour *et al.*, 2017); and (3) the use of identified DA-GABA neurons to learn how brains encode stimulus value (Jing *et al.*, 2007; Crossley *et al.*, 2018).

Surveying the literature on DA as a multifunctional neurotransmitter in gastropod molluscs, it is striking how many of its functions are shared with other taxa, including vertebrates (Table 1). Here, a sequence is proposed that traces the incorporation of DA into various functions as nervous systems became more complex and proficient, from its sensory role in appetitive food finding to its reinforcing role in appetitive conditioning. The presence of common dopaminergic functions across phylogeny implies the ancient origin of this se-

quence, possibly predating the split of the protostome and deuterostome lineages. Moving forward, advances emerging from the simpler gastropod systems should continue to inform, and be informed by, exploration of DA's multifunctional contributions to sensorimotor integration and behavioral plasticity across phylogeny.

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