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Review

Frank Beach Award Winner: Steroids as neuromodulators of brain circuits and behavior

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ABSTRACT

Neurons communicate primarily via action potentials that transmit information on the timescale of milliseconds. Neurons also integrate information via alterations in gene transcription and protein translation that are sustained for hours to days after initiation. Positioned between these two signaling timescales are the minute-by-minute actions of neuromodulators. Over the course of minutes, the classical neuromodulators (such as serotonin, dopamine, octopamine, and norepinephrine) can alter and/or stabilize neural circuit patterning as well as behavioral states. Neuromodulators allow many flexible outputs from neural circuits and can encode information content into the firing state of neural networks. The idea that steroid molecules can operate as genuine behavioral neuromodulators – synthesized by and acting within brain circuits on a minute-by-minute timescale – has gained traction in recent years. Evidence for brain steroid synthesis at synaptic terminals has converged with evidence for the rapid actions of brain-derived steroids on neural circuits and behavior. The general principle emerging from this work is that the production of steroid hormones within brain circuits can alter their functional connectivity and shift sensory representations by enhancing their information coding. Steroids produced in the brain can therefore change the information content of neuronal networks to rapidly modulate sensory experience and sensorimotor functions.

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What is neuromodulation and why is it so important?

The field of 'connectomics' has generated a great deal of interest and enthusiasm in the past few years. Connectomics has already begun to map out large-scale neural circuit diagrams, including ultrastructural analysis of the human brain (e.g., Amunts et al., 2013). These efforts include the US BRAIN Initiative, the Human Connectome Project, and the European Union Flagship Human Brain Project. The push to map brain circuits wholescale is essential for progress in neuroscience as it will provide unprecedented resources to neuroscientists. All the same, a

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complete map alone will not provide a comprehensive understanding of how brains function and which treatments may ameliorate neurological dysfunction (Bargmann and Newsome, 2014; Oh et al., 2014). In concert with the connectome, small molecules called neuromodulators provide a means to dynamically alter the functional connectivity of circuits in response to external and internal cues (Harris-Warrick, 2011; Marder, 2012). Understanding how circuits are modulated by small diffusible molecules remains a challenge that is particularly well-suited to neuroendocrinologists, given our interest in studying the interplay between neuroanatomy and hormones. Below, I summarize four key features of the classically-identified neuromodulators. I then evaluate how these properties can apply to our emergent understanding of steroid signaling in brain circuits.

Neuromodulators occupy an important temporal niche for signaling

Several decades of work on the nematode *Caenorhabditis elegans* have demonstrated both the explanatory power and the limitations of a completed brain wiring diagram. The neural connectome of *C. elegans* has been solved (Jarrell et al., 2012; Towlson et al., 2013). Each adult employs a maximum of 302 neurons to direct a variety of behaviors. Each neuron has an established identity across individuals, and the connectivity pattern of each identified neuron is also known. However, on 'top' of this map there are more than 200 distinct neuropeptides encoded by the *C. elegans* genome that can influence the nervous system and behavior (Bargmann, 2012). Thus, the extraordinary layer of signaling interactions via neuromodulation belies the relatively simple 'solution' of having the established wiring diagram in hand.

Unpacking how modulation works in the nervous system of *C. elegans* and other species with so-called 'simple' brains has solidified the view that neuromodulators are essential for temporally-flexible brain functions and behaviors. Because neuromodulators generally alter circuit function on the timescale of seconds-to-minutes, they help fill the 'signaling gap' between events that can be encoded by fast neurotransmission (i.e., on the timescale of milliseconds) and gene transcription and protein translation (i.e., on the timescale of hours/days). In other words, neuromodulators occupy an important temporal niche for signaling in the nervous system, nestled between fast neuronal action potentials and slower genomic action potentials (for thorough discussions of neuroendocrine and genomic action potentials see: Clayton, 2000; Hofmann, 2010).

Neuromodulators provide circuit flexibility and dynamic functional connectivity

The study of neuromodulation has relied heavily on understanding the inner workings of central pattern generators (CPGs). The clearest examples of CPGs in animals are the discrete, identified neuronal assemblages that are both necessary and sufficient for the control of rhythmic behaviors like feeding, locomotion, heart rate, vocalization, and respiration (Bass and Zakon, 2005; Feldman and Del Negro, 2006; Grillner, 2003; Marder and Bucher, 2001; Marder and Calabrese, 1996; Rhodes et al., 2007). The most comprehensive understanding to date of a CPG that exhibits circuit flexibility in response to neuromodulation comes from more than 40 years of investigations in the crustacean stomatogastric ganglion (STG). The STG is a small network of neurons that are identifiable across individuals, and for which the 'connectome' circuit diagram has also been solved. The handful of neurons within the STG constitute a central pattern generator (CPG) that drives the motor movements associated with digestion. These rhythmic behaviors are complex, highly variable, and sensitive to environmental cues in crustaceans (Harris-Warrick and Johnson, 2010; Marder and Bucher, 2007; Marder et al., 2005).

At any one moment the current CPG activation pattern (and hence digestion motor rhythms) can shift depending on the relative concentrations of neuropeptides and other modulators that are released into the STG (Kiehn and Katz, 1999; Kvarta et al., 2012; Marder, 2012). The shifts in the CPG activation pattern are due to changes in the strength and sign of individual synaptic connections in the STG network. For example, as shown in Fig. 1, in the absence of dopamine stimulation the 'AB' neuron drives rhythmic activity in both the 'VD' and 'PD' neurons (each neuron in the network is named, as each neuron is readily identifiable across animals). In the presence of 10^{-4} M dopamine the AB neuron switches on strong synaptic input to the LP neuron, and the synaptic inputs from the AB neuron to the PD and VD neurons are attenuated (Flamm and Harris-Warrick, 1986). The pattern of functional connectivity is yet again different in the presence of other neuromodulators like serotonin and octopamine (Fig. 1). Therefore, neuromodulators provide extraordinary flexibility in CPG network properties (Harris-Warrick, 2011; Harris-Warrick and Johnson, 2010).

In addition to the simple presence or absence of a given neuromodulator, the relative concentrations and mixture of neuromodulators at any one moment can provide yet another layer of dynamic functional connections within a circuit. For example, in the spinal CPG for locomotion, dopamine modulates locomotor activity in a dose-dependent manner, by directing opposite rhythms at low vs. high concentrations on the same CPG network (Clemens et al., 2012). Similarly, dopamine and other modulators can alter information transfer in basal ganglia circuits (i.e., between the cortex and thalamus) via dose-dependent actions in the striatum, illustrating how biogenic amines can dynamically shift functional connections in the vertebrate forebrain (Leblois et al., 2010).

Therefore, as a general principle, neural circuits do not have fixed connective properties. The relative weights of synaptic connections between neurons in a network are continually reconfigured by the presence and the relative, momentary concentration of neuromodulators.

Neuromodulators can change the information content of networks to shift sensory and motor representations

It is well-established that neuromodulators like dopamine are responsive to environmental cues. There has been particular interest in neuromodulators because they can provide learning or error-related signals to brain circuits. The vast literature on 'reward prediction error' and midbrain dopamine projections illustrates how one neuromodulator can dynamically influence the information contained in neural circuits regarding external/internal conditions, and thereby guide behavioral decisions (e.g., Glimcher, 2011; Schultz, 2013). This role for dopamine is not exclusively a vertebrate phenomenon. Many invertebrate organisms like Aplysia exhibit environmentally-contingent dopamine release that is involved in learning-induced plasticity via specific actions on a motor CPG (Bedecarrats et al., 2013). Therefore, one key feature of neuromodulators is that they can change the information content of a network, providing instructive signals and/or feedback inputs to influence ongoing circuit computations.

Sensory representations are particularly subject to neuromodulation. Many biogenic amines like dopamine, norepinephrine and serotonin can directly shift sensory representations through modulatory actions in the forebrain, midbrain, and thalamus (Devilbiss et al., 2006; Hoke and Pitts, 2012; Hurley and Sullivan, 2012; Jacob et al., 2013; Ramsey et al., 2010). In addition to sensory modulation, in the case of motor networks, the information content of ongoing motor patterns for behaviors is also sensitive to neuromodulation. These include the firing state of locomotor CPGs that can change in the presence of biogenic amines (Clemens et al., 2012; Kiehn and Katz, 1999).

Therefore, because neuromodulators can dynamically shift the information content of neural circuits, they can directly modify not only how the outside world is perceived but also how motor programs unfold to pattern behaviors.