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Review

Long-lasting changes in neural networks to compensate for altered nicotinic input

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ABSTRACT

The nervous system must balance excitatory and inhibitory input to constrain network activity levels within a proper dynamic range. This is a demanding requirement during development, when networks form and throughout adulthood as networks respond to constantly changing environments. Defects in the ability to sustain a proper balance of excitatory and inhibitory activity are characteristic of numerous neurological disorders such as schizophrenia, Alzheimer's disease, and autism. A variety of homeostatic mechanisms appear to be critical for balancing excitatory and inhibitory activity in a network. These are operative at the level of individual neurons, regulating their excitability by adjusting the numbers and types of ion channels, and at the level of synaptic connections, determining the relative numbers of excitatory versus inhibitory connections a neuron receives. Nicotinic cholinergic signaling is well positioned to contribute at both levels because it appears early in development, extends across much of the nervous system, and modulates transmission at many kinds of synapses. Further, it is known to influence the ratio of excitatory-to-inhibitory synapses formed on neurons during development. GABAergic inhibitory neurons are likely to be key for maintaining network homeostasis (limiting excitatory output), and nicotinic signaling is known to prominently regulate the activity of several GABAergic neuronal subtypes. But how nicotinic signaling achieves this and how networks may compensate for the loss of such input are important questions remaining unanswered. These issues are reviewed.

Contents

1. Introduction

A striking feature of neural networks is their ability to maintain input–output relationships, adjusting to accommodate in ways that sustain functional behavioral responses. Key here is the homeostatic nature of circuits, adjusting the excitatory-to-inhibitory balance (E/I ratio) across networks and within individual neurons comprising the circuits. Fundamental to this process is the threshold set within individual neurons for firing

Abbreviations: ACh, Acetylcholine; E/I, excitatory-to-inhibitory; LTD, long-term depression; LTP, long-term potentiation; nAChR, nicotinic acetylcholine receptor; α7KO, α7-nAChR constitutive knockout mouse; O–LM, oriens–lacunosum moleculare; PV, parvalbumin; 5-HT_{3A}R, serotonin receptor 3a; SST, somatostatin; VIP, vasoactive intestinal peptide.

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action potentials and the contribution of their output to network activity. A second level of regulation involves the number and ratio of excitatory versus inhibitory synapses a neuron receives. Deficiencies in the E/I ratio for networks in the brain overall emerge as a central feature in a number of neurological disorders, underscoring the importance of homeostatic regulation. Examples include epilepsy, schizophrenia, autism, and Rett syndrome [1–5].

Nicotinic cholinergic signaling is initiated early in development and extends across much of the central nervous system. It involves the neurotransmitter acetylcholine (ACh) activating a variety of ligand-gated ion channels termed nicotinic acetylcholine receptors (nAChRs). Because nAChRs are widely distributed and can elevate intracellular calcium levels locally, they can exert numerous modulatory functions in the nervous system. These include regulation of presynaptic transmitter release at a variety of synapses, as well as promotion of synaptic plasticity through a number of postsynaptic actions. The importance of nicotinic signaling during development is reflected in the fact that early exposure to nicotine is known to cause long-lasting behavioral changes seen in the adult [6–20]. The contributions of nicotinic signaling to homeostatic regulation and maintenance of the E/I ratio are only beginning to be understood. This review will first summarize the nature of E/I control, and then consider how nicotinic signaling influences fundamental features of the nervous system relevant for E/I balance, including its actions on interneurons. It concludes with a consideration of mechanisms employed by the nervous system to compensate for long-lasting alterations in nicotinic signaling.

2. Maintaining the excitatory-to-inhibitory balance in neural networks

Throughout the brain, excitatory and inhibitory synaptic inputs are tightly regulated with respect to number and function, balancing their effects against each other [21,22]. Network activity appears to be maintained within a given dynamic range (rather than at an exact point) by compensatory alterations, or 'synaptic homeostasis' [23–25]. This prevents runaway signaling while providing stable long-term effectiveness and integrity. The balance between excitation and inhibition in networks results from the coordinated and highly regulated activities of recurrent excitatory and inhibitory connections and governs numerous brain processes including, for example, integration of sensory information in the cortex [26–30].

Activity patterns within a network are shaped by the firing properties of individual neurons and the connections they make. The firing properties and electrophysiological characteristics of a neuron are, in turn, determined by the combination, spatial distribution, and density of ion channels and receptors expressed across the cell surface [31]. To maintain homeostasis in a constantly changing environment, neurons can employ a variety of mechanisms to regulate these individual features. Examples include activity-induced compensatory changes in the ratios of voltage-dependent ion channels and receptors [32–39], as well as activity-independent mechanisms [40]. Theoretical models predict that neurons with a common and well-defined electrophysiological phenotype can achieve this with very different contributions of channel conductances, having only weak correlations among the conductances [41]. Each measured electrophysiological property of the neuron with a given well-defined behavior can be achieved by a different subset of several maximal conductances, showing that there are many ways to arrive at the same overall outcome.

Another dimension of homeostasis is reflected in the balance of excitatory versus inhibitory input a neuron receives. An instructive example is provided by pyramidal cells of the cortex that display a fixed ratio of excitatory and inhibitory input, despite large variations in amplitude of the synaptic response. As a result, the two kinds of input remain proportional, thereby equalizing E/I ratios [22]. Interestingly, parvalbumin-positive interneurons play an important role in this, participating in a bidirectional modulation of their synaptic strength onto cortical neurons to accommodate altered excitatory input and achieve the proper E/I ratio. In contrast, somatostatin-positive neurons innervating the cortical neurons do not contribute to the equalization. These observations focus attention on interneuronal subpopulations as key for determining E/I ratio and sustaining appropriate activity levels of networks.

The nicotinic cholinergic signaling system is strategically positioned to exert neuromodulatory effects on the coupling of excitatory and inhibitory balance. In the visual cortex, endogenous cholinergic signaling helps regulate the E/I balance through both nicotinic and muscarinic mechanisms [42]. Nicotinic cholinergic signaling relies on a variety of nAChR subtypes, each with its own pharmacological and expression-pattern profiles. The receptors can be found both pre-and post-synaptically, as well as extra-synaptically, on excitatory and inhibitory neurons (and also on glia), where they produce a variety of actions. In the mammalian brain, the most abundantly expressed nicotinic receptors are the heteropentameric α4- and β2-containing nAChR (α4β2-nAChR) and the homopentameric α7-containing nAChR (α7-nAChR). The latter has a high relative calcium permeability [43,44], equipping it to have many downstream effects [45,46]. Both receptor types occur at relatively high densities in the cortex and hippocampus. Notably, nicotinic signaling is well placed to provide modulation that achieves fine-tuning of circuits to select parameters within the dynamic range of acceptable values. It will be important for future research to identify the "tipping point" within a circuit that takes neuronal activity out of its acceptable range [41,47–49].

3. Interneuron subtypes and nicotinic signaling

Inhibitory input is critical not only for sculpting specific firing patterns within a neural network but also for preventing network activity from escalating to dysfunctional levels. GABAergic interneurons are responsible for the vast majority of inhibitory signaling in the nervous system and are extremely diverse. They can be classified by a variety of criteria including location, anatomy, electrophysiological properties, and expression of distinct neurochemical markers. One classification separates GABAergic cortical interneurons into three largely non-overlapping groups based on expression of parvalbumin, somatostatin, or serotonin receptor 3a (5-HT_{3A}R). These categories include nearly all cortical interneurons [50], which account for about 20% of all neurons in the cortex [2]. Further subdivisions have combined markers such as parvalbumin, calretinin, calbindin, somatostatin, vasoactive intestinal peptide (VIP), and neuropeptide Y [51,52]. With the possible exception of CHRNA2, the gene for the α2-nAChR subunit, on oriens–lacunosum moleculare (O–LM) interneurons in the hippocampal CA1 region in rodent brains [53], no single molecular marker has been found to be unique for a given interneuron subtype.

Nicotinic input represents a prominent source of modulation for cortical interneurons, with major cholinergic projections coming from the basal forebrain [54–56]. Hippocampal interneurons, which range from 4 to 10% of the total neurons along the ventral–dorsal axis [57], also receive extensive cholinergic innervation, largely from the medial septum [58,59]. A variety of nAChR subtypes mediate the nicotinic input both in the cortex and hippocampus [60,61]. Prominent are α7-nAChRs which are expressed on a variety of interneuronal subtypes thought to include parvalbumin-positive, somatostatin-positive, and VIP-