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Long-lasting Changes in Neural Networks to Compensate for Altered Nicotinic Input

Danielle John[1,2] and **Darwin K. Berg**[1,2,*]

[1]Neurobiology Section, Division of Biological Sciences, University of California, San Diego, La Jolla, CA, 92093-0357

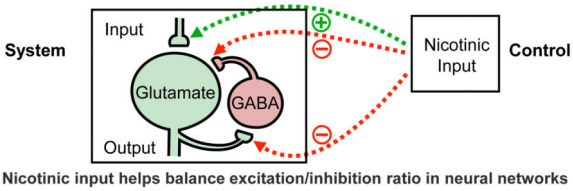
[2]Kavli Institute for Brain and Mind, University of California, San Diego, La Jolla, CA 92093–0357

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.

Graphical Abstract

[*]**Corresponding author:** Darwin K. Berg; Div. of Biol. Sciences; Univ. of Calif., San Diego, 9500 Gilman Drive; La Jolla, CA 92093-0357. **Tel:** 858-534-4680, **Fax:** 858-534-7309, dberg@ucsd.edu. .



Nicotinic input helps balance excitation/inhibition ratio in neural networks

Keywords

Nicotinic; homeostasis; compensation; neural network; E/I ratio; circuits

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 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.

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).

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 4-10% 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-positive interneurons, all of which have their own unique subset of connectivity patterns in cortical circuitry (62). The α7-nAChR is also expressed at high levels on interneurons in the hippocampus (63, 64). Anatomical reconstruction of interneurons in this region reveals heterogeneous populations of multiple subtypes, including those that inhibit pyramidal cells at somatic or dendritic synapses (65, 66). As a result, nicotinic activation of interneurons via α7-nAChRs could either inhibit or dis-inhibit hippocampal pyramidal neurons (the primary hippocampal output) depending on whether the activated interneuron synapses directly onto pyramidal cells or onto other interneurons that normally inhibit the pyramidal cells (67-69).

In addition to α7-nAChRs, many interneurons also express the other major nicotinic receptor subtype, namely the α4β2-nAChR. The relative abundance of receptor varies dramatically with neuron type (70), indicating a potential for lamina-specific neuromodulatory control of hippocampal function by nicotinic input. It remains unclear, however, how the number and distribution of α7-nAChRs and α4β2-nAChRs vary with interneuron subtype.

The diversity of GABAergic interneurons positions them to influence network function in complex ways (71-73). The interneuron population of the hippocampus is incredibly diverse with the precise roles played by distinct inhibitory cell types currently being unclear. Each subtype of hippocampal interneuron has distinct postsynaptic domains and is therefore positioned to differentially control input and output activity (71). Hippocampal basket and axo-axonic interneurons, both of which are parvalbumin-positive, are located in the stratum pyramidale region where they suppress pyramidal neurons via perisomatically suppressing Na^+ spikes and action potentials (51, 74). Most cortical somatostatin interneurons are Martinotti cells that send their axons into superficial layers and form dense axon collateral networks in layer I (75). They are morphologically and physiologically similar to O-LM neurons of the hippocampus (76), which are highly responsive to nicotinic signaling (53, 77). Little is known about the nicotinic responsiveness of cortical somatostatin neurons.

O-LM cells (somatostatin-positive) are found in the outermost layer of the hippocampus in the stratum oriens with perpendicular projections to the stratum lacunosum-moleculare (71), and they modify the excitatory drive to the distal apical dendrites of pyramidal neurons. Nicotinic activation or potentiation of O-LM neurons in CA1 facilitates long-term potentiation through increases in calcium influx (53, 78). O-LM cells have a key role in gating information flow in CA1, differentially modulating CA3 and entorhinal inputs to hippocampal CA1 neurons, are interconnected by gap junctions, receive direct cholinergic inputs from subcortical afferents, and are primarily responsible for the effect of nicotine on synaptic plasticity of the Schaffer collateral pathway (53). They are commonly identified by somatostatin, but somatostatin is also expressed by other interneuron subtypes throughout the hippocampal formation (71). Only in the hippocampal CA1 is CHRNA2 reliable as a specific marker for O-LM cells (53).

A subpopulation of interneurons highly responsive to nicotine is the 5-HT_{3A}R+ neurons that express VIP and are enriched in layer I of the cortex. Optogenetically it has been shown that VIP-positive cells express functional α4β2-nAChRs, but they represent an anatomically and electrophysiologically heterogeneous subgroup of cells (79). Unlike various other populations of interneurons, 5-HT_{3A}R+ neurons do not express either Lypd6 or Lynx1 at detectable levels (80). This is noteworthy because members of the Lynx family represent a unique set of nAChR modulators (54, 81). Two members – Lynx1 and Lypd6 – are expressed in discrete GABAergic interneuron subpopulations, with Lynx1 being expressed in most parvalbumin-positive neurons, while Lypd6 is only found in somatostatin-positive interneurons (80). The distribution and function of Lynx family members in modulating nicotinic input in neural networks will be an important issue for the future.

Synaptic mechanisms for maintenance of excitatory-to-inhibitory balance

If the first level of homeostatic control of network activity involves neuronal thresholds for firing action potentials, the second level would appear to be the ratio of excitatory and inhibitory input (E/I ratio) neurons receive. And, of course, critical here is whether the neuron being excited is itself excitatory or inhibitory and, if the latter, whether it inhibits excitatory neurons or other inhibitory neurons. Various methods have been used to assess the E/I input a neuron receives. One is to measure the frequency of excitatory versus

inhibitory synaptic events in single cells. Electrophysiologically this is usually assessed by comparing the relative contribution of glutamatergic and GABAergic synaptic events (82). Anatomical methods for identifying synapses utilize either immunostaining for glutamatergic or GABAergic synapses or ultrastructural analysis to quantify symmetrical (inhibitory) versus asymmetrical (excitatory) synapses on a neuron (82, 83).

Serial electron microscope reconstructions have shown that rat hippocampal CA1 pyramidal cell dendrites receive approximately 30,000 excitatory inputs and 1,700 inhibitory inputs, yielding an E/I ratio of about 18:1 (82). Examination of local inhibitory interneurons in the hippocampus reveal notable interneuron-subtype differences: parvalbumin-positive neurons contain about 16,000 inputs of which 6% are inhibitory (E/I = ~14:1); calbindin-positive neurons receive 4,000 inputs of which 30% are inhibitory (E/I = ~2:1); and calretinin-positive neurons maintain 2,000 inputs of which 20% are inhibitory (E/I = ~4:1; 84). Considerable differences in E/I ratios are discernable between, and even amongst, neurons of particular classes, and ratios may be highly dynamic over the entire course of development.

Absence of the α7-nAChR subtype, as found in the α7-nAChR constitutive knockout mouse (α7KO), results in decreased numbers of excitatory glutamatergic synapses forming with no change in the numbers of GABAergic synapses, assessed both electrophysiologically and by immunostaining. This suggests a decreased E/I ratio compared to wild-type control neurons, which was confirmed by a comparison of maximally evoked glutamatergic versus GABAergic synaptic responses in pyramidal cells of the hippocampal CA1 region (83). Unknown is whether this altered E/I is also found in interneurons and, if so, how it affects overall output of the CA1.

An interesting related question is whether various compensatory effects, e.g. alterations in the threshold for firing action potentials, compensate for the altered synaptic E/I ratio.

Development is a particularly challenging time for maintaining E/I balance as circuits are forming and becoming stabilized. Vast changes occur in anatomy, synaptic connections, and network dynamics. GABAergic signaling is initially excitatory/depolarizing in the immature brain, but as the brain develops it transitions to become inhibitory/hyperpolarizing as found in the adult (85, 86). An indication of the changing consequences for network function comes from the observation that during the early phase when GABA is excitatory/depolarizing, repetitive stimulation can attenuate long-term depression (LTD) in GABAergic inputs (87). In contrast, subsequently when GABA becomes inhibitory/hyperpolarizing, similar stimulation yields GABAergic long-term potentiation (LTP, 87).

Because the α7KO is constitutive, it would be expected to have effects throughout development, and this appears to be the case. Not only do the mice display fewer excitatory synapses at all times examined, but they also show a delay in the critical developmental transition when GABA converts from being excitatory/depolarizing to inhibitory/hyperpolarizing (88). A delay is also seen in the GABA transition for adult-born neurons in the α7KO dentate gyrus, and this is associated with reduced survival, maturation, and integration of the neurons (89, 90). Notably, immature granule cells in the postnatal dentate

gyrus have α7-nAChRs, raising the possibility that the nicotinic effect is a direct one (91). How nicotinic signaling promotes glutamatergic synapse formation and whether the system can compensate for synaptic deficits will be important questions for the future.

Nicotinic perturbation and pathological E/I imbalance

An imbalance in the E/I ratio, occurring early in development, is increasingly being associated with neurological disorders such as epilepsy, schizophrenia, autism, and Rett syndrome (1-5). Aberrations in nicotinic signaling, particularly via α7-nAChRs, are also increasingly being linked with neurological disorders, principal among them being schizophrenia (92), Alzheimer's disease (93, 94), and juvenile myoclonic epilepsy (95).

Deletion of human 15q13.3, including the α7-nAChR gene, is associated with autism, mental retardation, epilepsy, bipolar disorder, and intellectual disability (96-108). Additional evidence suggests that deletion of the α7-nAChR gene alone may be sufficient to cause the majority of the associated clinical features in patients with these disorders (100, 101, 104, 107).

Nicotinic signaling has long been implicated in schizophrenia. Some propose that schizophrenics self-medicate by smoking, with smoking prevalence reaching 90% (109). Post-mortem brain analysis of schizophrenic patients reveals loss of α7-nAChRs in both the prefrontal cortex and hippocampus (96, 110-114) and also deficits in both parvalbumin and somatostatin neurons (115-117), known to normally express these receptors. Alterations in α7-nAChR levels contribute importantly to the prominent changes in E/I ratio seen in schizophrenia. Rodent studies have shown that deletion of the α7-nAChR impairs cortical parvalbumin GABAergic interneuron development, and this mirrors many of the neurochemical characteristics found in the schizophrenic brain (118). The chromosome containing the α7-nAChR subunit gene is a site of heritability for schizophrenia, and also for a deficit in inhibitory neuronal function associated with this disorder. Taken together, current findings suggest that loss of interneurons expressing α7-nAChRs contributes to the pathogenesis of schizophrenia.

Neurological diseases involving aberrant nicotinic signaling and E/I imbalances are not restricted to developmental disorders. For example, the loss of excitatory cholinergic neurons in Alzheimer's disease, a neurodegenerative disorder typically with a late onset in life, results in an unbalanced E/I ratio (119). The loss of cholinergic neurons has a profound effect on nicotinic signaling, particularly on signaling through α7-nAChRs (120).

How nicotinic signaling in general, and α7-nAChRs in particular, affect E/I and related neurological disorders is not known. In α7KO mice, the numbers of parvalbumin-positive interneurons in the cortex are decreased compared to wild-type littermates (118). The decrease in α7-nAChR-expressing parvalbumin-positive interneurons could alter the E/I ratio if not compensated. Both parvalbumin and somatostatin neurons have been implicated in governing network oscillations in the brain (121, 122). Parvalbumin interneurons are thought to play a role in the synchronization of gamma network oscillations in the hippocampus (123). Optogenetic disruption of parvalbumin cell activity can abolish gamma

rhythm activity in cortical circuits (124). It is known that α7-nAChRs are required for control of gamma oscillations (125).

Nicotinic signaling is fundamental to an array of cognitive processes including attention, and learning and memory, whilst also contributing to synchronous oscillatory activity, as noted above (126-129). Network gamma oscillations are strongly correlated with cognitive activity such as working memory (130, 131) and sensorimotor gating, both of which are commonly affected in schizophrenia (81, 125, 131). Both dysfunction of parvalbumin-positive neurons in schizophrenia (5) as well as microdeletion of 15q13.3, which includes the loss of the α7-nAChR gene and is itself linked to schizophrenia (108), have been associated with perturbed gamma oscillations. Consistent with the above, α7KO mice have deficits in cortical parvalbumin interneurons (118) and show dysfunctional gamma oscillations (132).

What role might homeostatic compensation play in systems with aberrant nicotinic signaling? Deficits in behavior may not represent failure of homeostatic compensation. In fact, homeostatic compensation can result in a number of different outcomes, depending on the challenge. The homeostatic process may be working correctly but still produce pathology in response to particular perturbations or deletions (47). Using computer modeling, it has been shown that very similar network activity can be achieved with disparate circuit parameters (133), and it has been experimentally confirmed that alterations in the expression of one channel can be compensated by changes in the density of one or more other channels (40). Compensation, following genetic manipulation, can keep the network functioning within an optimal operating range (39) and prevent runaway changes that could be deleterious. As a result, compensation could produce considerable animal-to-animal variability in network parameters whilst still allowing for appropriate overall network performance (48, 49). In the case of α7KO mice, this could help explain why significant deficits in E/I ratios inferred from synaptic connections (83) produces a relatively mild behavioral phenotype (134, 135).

Conclusions

Nicotinic cholinergic signaling clearly plays important roles both during development in shaping the neural networks that form and in the adult where it modulates network function in numerous ongoing ways. Extended aberrations in nicotinic signaling have been implicated in a number of neurological disorders, and, of course, direct exposure to nicotine can produce addiction. How the nervous system responds to these challenges is only beginning to be understood. It is clear, however, that compensatory mechanisms are likely to be activated and that these can take multiple forms, at least theoretically, to ameliorate consequences, such as those disturbing the E/I balance in the network. As noted above, some of the compensatory changes in pursuit of homeostasis may unavoidably produce deleterious consequences, while others may at least partially return the system to a normal operating range. Important challenges for the future will be elucidation of network consequences when nicotinic signaling is disrupted in a sustained way and, perhaps even more interesting, will be the discovery of compensatory mechanisms the nervous system employs in an attempt to recover homeostasis in the absence of nicotinic signaling.

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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
nAChR	nicotinic acetylcholine receptor
O-LM	oriens-lacunosum moleculare
PV	parvalbumin
5-HT$_{3A}$R	serotonin receptor 3a
SST	somatostatin
VIP	vasoactive intestinal peptide

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