
REVIEW ARTICLE

What Has Intrinsic Signal Optical Imaging Taught Us About NGF-Induced Rapid Plasticity in Adult Cortex and Its Relationship to the Cholinergic System?

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Abstract

Intrinsic signal optical imaging (ISI) is a high-resolution functional brain mapping technique that is being used to further our understanding of the neocortex and its interaction with drugs. Recent studies using combination ISI and *in vivo* pharmacology have advanced our insight into the actions of both acetylcholine and neurotrophins on inducing rapid and large-scale cortical plasticity. In particular, it appears that acetylcholine (ACh), nicotinic ACh receptors, nerve growth factor (NGF), and NGF receptors (TrkA and p75) are involved in an important feedback loop between the basal forebrain cholinergic system (BFCS) and the neocortex. Specifically, recent data suggest that NGF expressed in the cortex may act on multiple time scales on the BFCS: acutely to increase BFCS release of acetylcholine, intermediately to induce sprouting of BFCS axons, and long-term to change gene expression of BFCS neurons. In this article, advances in understanding the links *in vivo* between the BFCS, neocortex, nicotinic ACh receptors, and NGF are reviewed.

Key words: Intrinsic signal optical imaging, Somatosensory, Barrel, Cortex, Nerve growth factor, Neurotrophins, Acetylcholine, Nicotine, Functional, Brain, Basal forebrain

Introduction

Background

A major goal in neuroscience is to understand brain function and how such function is modified by the action of drugs. *In vitro* techniques have given us significant information on the workings of individual neurons and the effects of drugs at neuronal synapses. However, to fully understand how drugs modify brain function, *in vivo* techniques are required, but until recently *in vivo* techniques either suffered from poor spatial resolution or could only

examine the actions of individual neurons. Intrinsic signal optical imaging (ISI) enables visualization of widespread cortical function with very high (micrometer) spatial resolution [1]. This imaging technique visualizes brain activity by the fact that in the cortex, active areas become darker compared with nonactive ones. Thus, activity patterns translate to light-reflectance patterns that can be detected by a sensitive camera. These evoked-activity changes in light-reflectance are called *intrinsic signals*, and the source of the signals are dependent on the wavelength of light imaged. A commonly used signal is the oximetric signal, which occurs because active neurons have an immediate need for oxygen, which leads to a rapid increase in deoxyhemoglobin concentration, and as deoxy-

hemoglobin has a different reflectance pattern than oxy-hemoglobin, this leads to a darkening of the cortex in the active area [2]. For more details on optical imaging techniques and their applications, see recent review [3]. As a specific example of the usefulness of this imaging technique, in this paper we will review how recent data from *in vivo* ISI studies have complemented results from *in vitro* studies and thus furthered our knowledge of the interactions between the basal forebrain cholinergic system (BFCS) and nerve growth factor (NGF).

Neurotrophins and Their Traditional Roles

Neurotrophins are a family of growth factors that consists of at least four well-characterized members: NGF, BDNF, NT-3, and NT-4/5. Their receptors belong to the high-affinity Trk family of tyrosine kinase receptors, but all neurotrophins also bind to the low-affinity p75 receptor [4–8]. These neurotrophins and their receptors play essential roles during the development of the nervous system by controlling programmed cell death, survival, and differentiation of neurons. Originally posited by Levi-Montalcini, three assumptions, collectively known as the *neurotrophic hypothesis*, underlie the neurotrophins' roles in the developing nervous system [9–13]. First, neurons depend on the availability of trophic factors for survival and, subsequently, for the persistence of their target connections. Second, target tissues synthesize and make available appropriate trophic factors to developing neurons. Third, targets produce trophic factors in limited amounts; consequently, the survival of developing neurons and the persistence of neuronal connections depend on neuronal competition for the available factor [9–13]. While the predictions of the neurotrophic hypothesis have been confirmed for NGF in the peripheral nervous system, more recent data in adult central nervous system suggest that NGF has a much larger role than as only a trophic factor, but in fact is also a rapid modulator of plasticity between the BFCS and the neocortex [14–16].

NGF's Role in Cortical Plasticity

Extensive evidence exists for the importance of neurotrophins in the normal development of the cortical structure and function [12, 17–20], and NGF in particular [21–28]. Nerve growth factor has been implicated in the cortical plasticity observed after monocular deprivation (by closing or silencing one eye), a popular model of experimentally induced developmental plasticity of the visual system. Recent evidence supports the endogenous presence of NGF in the *adult* cortex and the presence of its receptors on cells from the BFCS. In addition, using the functional imaging technique of ISI, NGF has been shown to rapidly (within minutes) augment functional activity *in vivo* in the adult cortex [15, 16]. Together, these data suggest new roles for NGF in the adult cortex in addition to its traditional

roles implied by the neurotrophic hypothesis. Specifically, NGF expressed in the cortex may act on multiple time scales on the BFCS: acutely (seconds to minutes) to increase BFCS release of acetylcholine, intermediately (minutes to hours) to induce sprouting of BFCS axons, and long-term (hours to days) to alter gene expression of BFCS neurons. How *in vivo* functional imaging data and *in vitro* data come together in support of this hypothesis is the topic of this review.

NGF's Role in Rapid Induction of Adult Cortical Plasticity *In Vivo*

NGF is Present in Cortical Neurons and Can Be Released by Neuronal Activity

Using antibodies that specifically recognize NGF, NGF was found endogenously within cells in the cortex and was unevenly distributed [29]. Nerve growth factor was dense in layers II–III and V–VI and sparse in layers I and IV. While there is no evidence yet for activity-dependent release of NGF *in vivo*, activity-dependent release of NGF was demonstrated *in vitro* in hippocampal slices [30, 31]. Such activity-dependent release was detected all along the neuronal process but was strongest in the dendrites, a major target of synaptic input to cortical neurons.

In Vitro Evidence for Rapid NGF Induction of Cortical Plasticity

The presence of NGF in the adult cortex has been thought to serve long-term processes, such as survival and maintenance of neurons, as an extension of its role during cortical development. However, evidence has accumulated to suggest that NGF may play other roles within the adult cortex that result in more immediate effects such as increasing synaptic efficacy. In slices of rat visual cortex within five to fifteen minutes after application, NGF induced a rapid increase in the amplitude of impulse-evoked excitatory postsynaptic currents through alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and *N*-methyl-D-aspartate (NMDA) receptors [32]. Adult cortical cell cultures showed activation of calcium-dependent potassium channels by NGF [33]. The time course of these effects was concentration-dependent, ranging from 10 to 30 minutes after application. The above *in vitro* evidence indirectly suggests that NGF may also play a rapid *in vivo* role in adult cortical plasticity.

In Vivo Evidence for NGF Induction of Rapid Cortical Plasticity

Exogenous application of NGF to the primary somatosensory cortex can induce dramatic and rapid changes in its functional properties *in vivo*. Using ISI to assay the effects of NGF on somatosensory cortical function, NGF applica-

tion was found to significantly augment a whisker functional representation by increasing its size and strength [15, 16]. Furthermore, these changes are detected within minutes after NGF application. Application of other neurotrophins such as BDNF had effect opposite to NGF [14, 15], and NT4/5 had no effect on the cortex [14], suggesting that NGF induction of cortical plasticity is not due to a generalized neurotrophic effect. This provided direct evidence for NGF's ability to affect neuronal activity rapidly *in vivo* in the adult cortex. One possibility may be that NGF is acting directly on cortical neurons to increase excitatory activity or decrease inhibitory activity, or both. However, high-affinity NGF receptors are not localized on cortical cell bodies, but rather they are localized on fibers projecting to the somatosensory cortex from the basal forebrain [15, 16].

Involvement of BFCS in the Rapid NGF Induction of Adult Cortical Plasticity

Basal Forebrain—General Background

The basal forebrain (BF) in the rat, known as the magnocellular basal forebrain nuclei, includes cells located in the medial globus pallidus, substantia innominata, and the septal nucleus of the diagonal band of Broca [34–36]. Cholinergic cells within this system project to the entire rat cortex [37] in a loose topographically organized manner [38, 39] and constitute the only known cholinergic projection to the adult cortex [40]. After release, ACh can influence target cells in the cortex through two broad classes of cholinergic receptors: muscarinic and nicotinic receptors. Muscarinic receptors seem to be associated with the BF-to-cortex system, although there may also be some nicotinic contribution in the first milliseconds following BF stimulation [41, 42]. However, as BFCS-induced plasticity in the cortex was demonstrated to be typically related to activation of muscarinic receptors, the potential contribution of nicotinic receptors is not clear. Indeed, nicotinic receptors in the rat somatosensory cortex do not appear to be associated with BF efferents [43], but are associated with thalamocortical input to layers I and III/IV of the adult rat [44], and with inhibitory interneurons [45]. Taken together, the role of nicotinic receptors in the activation of the cortex by the BFCS is still controversial. ACh's action through the muscarinic receptors is better characterized. ACh binding to the postsynaptic neuron leads to voltage-dependent block of potassium currents, resulting in a slow depolarization that is relatively long-lasting and facilitates the firing of pyramidal neurons in the cortex [46].

BFCS Role in Adult Cortical Plasticity In Vivo

Accumulating evidence suggests that ACh release in the adult neocortex can promote neuronal plasticity [42, 46–49].

Cells that were not responsive to a tactile stimulus in the rat somatosensory cortex started responding if treated with ACh [50, 51]. BFCS projections are capable of providing sufficient ACh release in the cortex to produce results similar to the ones obtained by the enhancement of evoked potentials [52, 53] or single-unit responses [54] after pairing the cutaneous stimulation with direct stimulation of the BF. Control experiments using atropine, a muscarinic receptor blocker, either by systemic delivery or local iontophoretic administration, showed that the effects described above were specific and dependent upon the release of ACh. A role for endogenous ACh release on evoked activity was also shown with ISI: topical application of scopolamine (a cholinergic antagonist similar to atropine) to rat somatosensory cortex contracts a whisker functional representation [55]. Furthermore, plasticity in the rat somatosensory cortex induced by a conditioning paradigm between whiskers is prevented by microiontophoresis of atropine [56]. In addition, lesions in the BF system can eliminate cortical plasticity. For example, lesions of BF in cats prevented the increase in the 2-deoxyglucose (2-DG) labeling that normally accompanies the reorganization of the limb representation in the somatosensory cortex following amputation [57, 58]. Similar BF lesions in rats produced similar results, but these rats were also significantly impaired in their ability to perceive whisker stimulation [59]. As the entire BF was lesioned in these experiments, and the BF contains at least three components (the BFCS, GABAergic projection neurons, and a third less well-defined, but likely glutamatergic projection system) [60], it is not clear whether these results are specifically related to the BFCS component of the BF. However, rats lacking the BFCS after treatment with a toxin specific to the BFCS (192-IgG saporin) failed to develop somatosensory plasticity that is normally induced when only two whiskers remain (“whisker pairing” plasticity) on the snout of the adult rat [61].

Given that the BFCS is implicated in somatosensory cortical plasticity, it is worth discussing briefly the events that may lead to the endogenous release of ACh by the BF. It is commonly believed that the BFCS is involved in attentive behavior, learning, and memory. The BF system is uniquely positioned to provide the cortex with information about the behavioral importance of a particular stimulus because it receives input mostly from the limbic and paralimbic structures [40]. Electrophysiological recordings in the BF supported this notion as it was demonstrated that cells in the BF are active as a function of the behavioral significance of a stimulus [62, 63]. Also, the BF is most known for its participation in acquisition of learning and memory [49, 64]. However, this general notion was challenged by the use of more selective lesions of the cholinergic BF that implicated the BFCS only in tasks that require selective attention [65]. Taken together, the above evidence suggests that after evaluating the behavioral significance of a stimulus, BFCS activity increases the release of ACh and thus enhances cortical plasticity.

Relationship Between NGF and the BFCS

NGF's Role in Maintenance of the BF

Nerve growth factor is synthesized by the target cells of BF projections in the cortex, binds to NGF receptors located on the BF nerve terminals, and is retrogradely transported to cell bodies of BF neurons, regulating their survival and functions as predicted by the neurotrophic hypothesis [12, 66, 67]. Extensive evidence exists for the neurotrophic hypothesis in the developing central nervous system between NGF and the BFCS [12]. Evidence also exists to support the notion that NGF continues to play a maintenance function for the BFCS after the brain matures. Exogenous application of NGF can rescue axotomized BF cholinergic cells, reverse the decline in cortical function, and restore memory [68–74]. On the time scale of weeks, NGF can restore a whisker functional representation after BF lesioning [75, 76]. More direct experimental proof for the role of endogenous cortical NGF in the maintenance of the BFCS [77] was obtained by local injections of anti-NGF antibodies into the cortex of the adult rat [78]. These experiments demonstrated a lack of ACh release in the cortex, disruption of connectivity between cortex and BF, and disruption of learning and memory. The importance of endogenous cortical NGF was also confirmed by the use of mutant mice [79]. Heterozygous mutant mice for the NGF gene showing a reduced level of both NGF mRNA and protein within the cortex had significant learning and memory problems that were accompanied by a loss and shrinkage of BF cells. Infusion of NGF in these adult mutants abolished the memory deficits and corrected the deficits in both size and projection density of BF cells to the cortex.

NGF-Induced Fast Release of ACh

Although it is clear that NGF plays a role in maintaining the BF cholinergic projections to the cortex, two key findings have introduced the possibility that NGF can induce immediate release of ACh. *In vitro* evidence for NGF-induced rapid release of ACh in the cortex was demonstrated in synaptosomes prepared from the rat hippocampus that included BF projection fibers [80]. Enhanced ACh release from these synaptosomes was found starting within one minute after NGF application. Anti-NGF antibodies blocked the NGF-induced rapid release of ACh. The rapid induction of ACh release cannot be readily explained by NGF's known role of regulating the survival and function of the BF cholinergic system, as this role requires a longer window of time (hours to days) to have its effects. In addition, the rapid release of ACh further supports the existence of NGF receptors on the terminals of BF projection fibers for which other direct [16] and indirect evidence exists [15, 81, 82]. The rapid induction of ACh release by NGF was also confirmed in synaptosomes prepared from the visual cortex of rats and further demonstrated that such induction of ACh release involves the

activation of the high-affinity TrkA receptor and the low-affinity p75 receptor [83]. These *in vitro* findings were corroborated *in vivo* in ISI experiments which demonstrated NGF's ability to rapidly (within minutes after application) augment a whisker functional representation [15, 16]. Furthermore, NGF's site of action was not directly on the neurons within the somatosensory cortex but rather from the BFCS projection neurons because TrkA receptors were found to be localized to BFCS cortical projections [16]. In addition, NGF's rapidly induced plasticity was not observed with ISI in a cortex with the BFCS lesioned by 192-IgG saporin [16]. These results demonstrated that topical application of NGF acts directly to enhance acetylcholine from BFCS terminals within the cortex and thus suggest that endogenous NGF released by activated cortical neurons could do the same.

Is There a Nicotinic ACh Receptor Specificity for NGF's Rapid Effects?

Intraventricular infusion of NGF in Alzheimer's patients was found to increase nicotine uptake and binding [84]. Data from hippocampus further suggested a specificity between the interaction of nicotine and NGF because nicotine receptor stimulation selectively upregulates NGF levels [85, 86]. Interestingly, ISI data also suggest a nicotine-dominated action of NGF. Nicotine application augmented a whisker functional representation with a time course that was nearly identical to NGF (although activation of muscarinic acetylcholine receptors can also increase the size of a whisker functional representation and enhance neuronal activity, therefore, a muscarinic component to NGF's actions is also probable) [16, 55]. Indeed, when NGF or nicotine induced their rapid plasticity following topical application to the cortex, their highest concentration was detected in layer I [15, 16, 55]. These findings suggest that NGF-induced rapid plasticity could act predominantly through activation of nicotinic cortical receptors within layer I. This suggestion is supported by findings that demonstrate that while nicotinic receptors can be found in all layers of the adult rat somatosensory cortex they are heavily concentrated in layer I [44, 87]. Indeed, evidence demonstrates directly that ACh affects neuronal activity in layer I through nicotinic receptors by showing that almost all of layer I interneurons can be excited by ACh nicotinic agonists. Furthermore, by activating selectively the nicotinic receptors of layer I interneurons, it was demonstrated that the predominant role of these interneurons is to inhibit layer II and III nonpyramidal cells, most likely GABAergic interneurons, and thus probably cause a disinhibition of cortical networks [45]. These authors further demonstrate that some of layer I interneurons have indeed direct axonal projections to cortical layers II and III. Indirect activation of layers II and III from layer I has also been demonstrated. Stimulating layer I has been found to induce long-term potentiation in layer II/III of the cortex indirectly via the cholinergic processes that also reach layer I [88]. Taken together, cholinergic activation of layer I by

NGF can cause large-scale cortical plasticity in deeper cortical layers through direct and indirect mechanisms that could act in concert and seem to be the result of activation of layer I nicotinic receptors. Furthermore, given that in layer I NGF is relatively sparse—but not TrkA, nicotinic receptors, or cholinergic fibers—*exogenous* NGF likely can efficiently induce plasticity. In the other cortical layers, there is more endogenous NGF, and thus activity-dependent release of *endogenous* NGF can efficiently induce plasticity.

Conclusions

Overall, the current data lead us to a general hypothesis which is described in detail in Fig. 1. Briefly, endogenous

NGF is released in an activity-dependent manner from cortical neurons, which in turn leads to increased ACh release from the BFCS, the ACh then further increases cortical activity. The increased cortical activity in turn elicits further release of neuronal NGF, and so forth, in a positive feedback manner aimed to amplify the effects of a behaviorally significant stimulus and, consequently, enhance functional plasticity in the cortex. The eventual shutting down of this feedback loop is achieved when the cortex is no longer stimulated with the behaviorally significant stimulus.

This loop is likely more complex than depicted in Fig. 1 as the distribution of neurons and neuronal processes vary across the different cortical lamina, as well as NGF, NGF

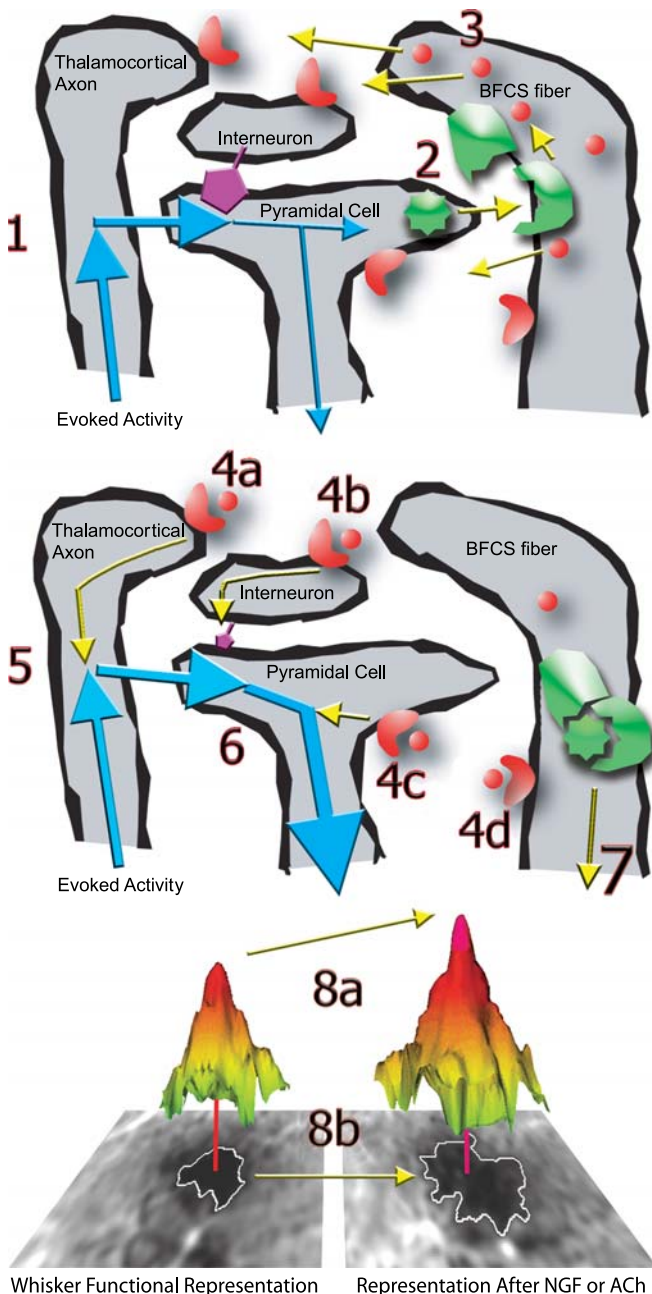


Fig. 1. Schematic of hypothesis for mechanism of NGF-induced cortical plasticity in the adult. (1–7) depict the events at the cellular level, (8) depicts the cortical population level. (1) Sensory stimulation activates a thalamocortical neuron, which in turn activates a cortical pyramidal cell. GABAergic interneurons inhibit these circuits (lavender). (2) Activity in the pyramidal cell leads to activity-dependent release of NGF (green) into the intracellular space where it binds to TrkA and/or p75 (green) on a BFCS fiber. (3) Binding of NGF to TrkA leads to rapid internalization of the complex as well as rapid release of acetylcholine (ACh, red). (4) ACh (or even choline [97, 98]) binds to receptors (red) on (a) $\alpha 7$ receptors on thalamocortical axons, (b) nicotinic receptors on interneurons (causing disinhibition [lavender]), (c) muscarinic receptors on pyramidal cells, and (d) ACh receptors on BFCS fibers themselves may also have a role. (5) Subsequent evoked thalamic activity now would be enhanced. (6) Subsequent activity within the pyramidal cell is also enhanced, leading to a more vigorous response to sensory stimulation. (7) The still-active NGF–TrkA–p75 complex is transported back along the axon where it may induce axonal sprouting and ultimately to the BFCS cell body where other trophic responses occur, such as regulation of cell body size and gene expression [12, 99, 100]. Below, on the cortical scale, ISI data from exogenous application of NGF or nicotine to the cortex [15, 16, 55] further suggest that endogenous NGF or ACh may augment the population response. A whisker functional representation is depicted in two and three dimensions. The black patches and corresponding red peaks depict the maximal strength of cortical activity and are shown superimposed on a picture of the cortex (white streaks are blood vessels). The white borders depict the size of the representation. (8) NGF or ACh by acting on multiple cells and synapses augments a whisker functional representation, specifically by (a) increasing the response of previously active neurons and/or recruiting the activity of nearby neighboring neurons that were previously inactive, thus *strengthening* the functional representation, and (b) bringing neurons previously at sub-threshold to threshold activity and thus also *expanding* the functional representation.

receptors, ACh, and ACh receptors. For example, NGF is unevenly expressed in neurons throughout the cortex [15, 29, 89], and the apical dendrites of most of these neurons extend to layer I [90, 91]. Thalamocortical axons project predominantly to layer III/IV but also to layers I and VI [92]. Both BFCS fibers [37–40] and inhibitory neurons [90] are found in all six layers of the cortex, and, therefore, steps of this loop may have different effects in different layers depending on which components are present in that cortical layer.

What is the biological significance of such a feedback loop? The cortex-to-BFCS feedback loop may provide a mechanism for the cortex to regulate its own plasticity. The traditional view regarding BFCS and cortex relationships assumes a “bottom-up” approach where the cortex is a passive recipient of the BF cholinergic influence following a behaviorally significant stimulus. If our hypothesis is correct, it will add a “top-down” or centrifugal component to the control of the BF–cortical system. Adding the centrifugal component would change the nature of the BF–cortical system from a passive to an *interactive* one, enabling the cortex to regulate and modulate BF activity. Such an interactive process would be conceptually similar to the process found in the pathways that transmit sensory information to the cortex. All major sensory pathways to the cortex (bottom up) also contain a massive centrifugal connection from the cortex (top down) that enables the cortex to regulate and modulate sensory information before it reaches the cortex [93]. This hypothesis provides a mechanism that could explain how the cortex could regulate its own plasticity. For example, such self-regulation of plasticity may provide a means for the cortex to enhance rapidly the effects of sensory input that has important behavioral value. Thus, our hypothesis may provide a fundamental insight to the cellular and molecular mechanisms by which the cortex could potentially regulate its own plasticity and to the nature of cortical plasticity in general. For example, future studies could examine whether the cortex has similar top-down regulation over other modulatory systems, such as the dopaminergic, noradrenergic, serotonergic, and histaminergic systems. As cortical plasticity is implicated in many fundamental processes of the brain, ranging from recovery after injury to learning and memory [20, 94–96], there is a growing need to better understand the mechanisms underlying such plasticity.

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