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Review

Smoking, nicotine and visual plasticity: Does what you know, tell you what you can see?

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ABSTRACT

Nicotine exposure alters activity-dependent synaptic plasticity processes. Effects on learning and memory outcomes, and the synaptic changes that underlie them, are well-documented. Parallels in hippocampal and visual system pharmacology suggest that nicotine has the potential to alter activity-dependent structural organization in visual areas. Such alterations may contribute to deficits in visual performance reported in smoking exposed individuals.

Contents

Almost a third of the world's adults smoke tobacco [58,76]. Smoking exposes the brain to nicotine, a small psychoactive molecule that is the primary addictive component of tobacco products [6]. Nicotine causes addiction by changing the synaptic efficacy of connections within specific reward centers in the brain. These changes have as their basis such cellular events as subtype specific receptor desensitization and up regulation, enhanced neurotransmitter release, potentiation of excitatory transmission, and depression of inhibitory inputs [58,76]. In recent years it has become clear that the ability of nicotine to cause long-term alterations in brain functioning is not limited to reward centers: other brain areas that are dependent upon activity to strengthen and organize the synaptic connections that underlie function can be affected.

1. Nicotine and learning and memory

The association of cholinergic dysfunction and a loss of nicotinic receptors with Alzheimer's disease helped motivate studies on the effects of smoking on cognitive function. Initial studies seeming to show a lower incidence of Alzheimer's disease among smokers [52] fueled work investigating the effects of smoking and nicotine on learning and memory. These studies have demonstrated that chronic nicotine treatments improve performance on a variety of memory tasks in both smokers and non-smokers. For example, transdermal exposure of individuals to nicotine improves short-term verbal memory and immediate and delayed recall [66,97]. Furthermore, acute treatment of Alzheimer's patients with either nicotine or novel nicotinic agents can improve the acquisition and retention of verbal and visual information [69]. Work in animal model systems supports the general conclusion that treatment with nicotinic receptor agonists improves memory while administration of nicotinic receptor antagonists impairs it [44,72]. Consequently, the hope that targeting nicotinic receptors will give rise to cog-

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nitive therapies persists [69]. However, this hope has now been disassociated from the act of smoking itself as reports of a positive association between smoking and cognitive function have been largely discredited. Heavy smokers experience deficits in working memory [26,27] and both new studies and a re-analysis of the previous ones clearly demonstrate that smoking increases the risk of Alzheimer's and may even accelerate cognitive decline in nondemented elderly [4,53,74].

In order to understand how nicotine augments learning and memory processes, its effects have been investigated at the cellular level. Acute nicotine administration enhances long-term potentiation (LTP) mechanisms in the hippocampus that are thought to be responsible for the acquisition and recall of some tasks [31,63]. In the CA1 region, where LTP is mediated by NMDA receptor activity, *in vivo* nicotine exposure induces a long-lasting enhancement of NMDA receptor currents [101]. Activation of presynaptic nicotinic receptors to increase glutamate release, as well as both a decrease in GABA-mediated inhibition and a direct depolarization of the postsynaptic pyramidal cells, contribute to an also observed short-term enhancement of NMDA receptor currents by nicotine [46,100]. Both α-bungarotoxin sensitive and insensitive nicotinic receptors are present in the hippocampus [86,94] and appear to be important to memory outcomes. Blockade of specific nicotinic receptor subtypes by infusion of antagonists into either the dorsal or ventral hippocampus impair working memory function [54,72]. While the location of nicotinic receptors on hippocampal elements is still being determined, it appears that α7-containing (α-bungarotoxin sensitive) and α4β2 (α-bungarotoxin insensitive) nicotinic receptors are present at presynaptic sites where they control glutamate release from afferent fibers and interneurons, respectively [3,35]. In addition, both receptor types are differentially distributed on GABA-containing interneuronal populations [2]. Alpha7-containing nicotinic receptors are also found postsynaptically on pyramidal cells (see Fig. 1) [41,46].

The abundant cholinergic input found in the hippocampus also characterizes thalamic and cortical brain regions [99]. By broadly modulating neuronal activity, acetylcholine is thought to play a major role in regulating both attention and sensory processing [59,87]. The heterogeneous family of nicotinic receptors is essential to this regulation and gives exogenous nicotine introduced into the system the potential to drastically alter activity patterns. Such alterations could have long-lasting consequences in plastic brain regions that, like the hippocampus, are dependent upon activity to change synaptic connection strength and/or organization. The visual system is composed of a number of such regions.

2. Nicotine and visual plasticity

Neural plasticity has been examined extensively in the visual system where activity-dependent synaptic plasticity results in the structural organization of afferent terminals [8,82,90]. Here, the effective depolarization of a postsynaptic target stabilizes the active synapses and the processes upon which those synapses reside; failure to stabilize these synapses induces the retraction of the processes which bears them [1,83]. The coupling of effective depolarization to synapse and branch stability allows for an exchange of presynaptic and postsynaptic partners until a suitable match is found. The visible outcome is a segregation of afferents into eye-specific layers in the lateral geniculate nucleus or eye-specific columns in the visual cortex. That nicotinic receptors play an essential role in these segregations is suggested by experiments in which a null mutation of a specific nicotinic receptor subunit prevents the formation of eye-specific zones [81]. Besides being present in the retina, this subunit is also found at high density in the superior colliculus [62]. It is also a component of all of the multiple nicotinic receptor subunits present in the optic nerve and that are thought to be transported to presynaptic sites in both the superior colliculus and lateral geniculate [15].

In addition to the separation of terminals carrying information from one eye from those conveying input from the other, the retinal afferent projections are also mapped onto their appropriate brain targets such that neighboring regions of the target receive information from neighboring regions of visual space [17,82]. The topographic maps that are created are thought to be essential for such functions as depth perception, object recognition, reconstruction of a visual scene and visual guidance of behaviors [7,16,47,67,98]. The mapping process has been studied extensively in the optic tectum, the non-mammalian vertebrate homologue of the superior colliculus [82]. Point-to-point order in the map of retinal ganglion cell terminals onto the tectum is mediated by NMDA receptor activity [14]. Treatment of the tectum with nicotinic receptor antagonists also blocks point-to-point map refinement, demonstrating a dependence of the process upon nicotinic receptor activity [93].

The pharmacology of the visual system is strikingly similar to that of the CA1 region of the hippocampus in a number of aspects (Fig. 1). First, in both systems glutamate is the main neurotransmitter released by the presynaptic inputs onto their targets. Second, *N*-methyl-D-aspartate (NMDA) receptor activity on those targets mediates an activity-dependent change in synapse strength and/or stability [70,82]. Third, multiple subtypes of nicotinic receptors are present and located predominantly on presynaptic terminals [11,34,50,77,78]. Activation of these receptors controls the release of glutamate within the target structures [35,75,91,103]. And finally, the presence of some nicotinic receptors on some of the postsynaptic cells themselves allows for a direct modulation of target depolarization levels [46,80,103].

Given these similarities, it is perhaps not surprising that the visual system is sensitive to nicotine exposure. The frog optic tectum has been chronically and selectively exposed to a number of pharmacological agents by embedding these substances into a slow release plastic and then implanting slabs of this plastic against the tectal surface [14,93,103]. Chronic treatment of this structure with nicotine alters map topography by reducing the area of retina projecting to a given tectal site (Fig. 2) [102]. This happens in the absence of any apparent cell death. This reduction can also be achieved by exposure to agonists specific to either α-bungarotoxin sensitive or α-bungarotoxin insensitive nicotinic receptors. Exposing the system to a general nicotinic receptor antagonist or to antagonists specific to each of the two nicotinic receptor subclasses drives map topography in the opposite direction. The developing optic tectum appears to be more sensitive to nicotine exposure than the mature tectum in that a lower concentration of the drug (8 μM) is effective in reducing the visual field area from which a tectal site receives input. Interestingly, treatment of the developing tectal surface with the lowest nicotine concentration demonstrated to have an effect on map topography in the adult (33 μM) produces a result opposite to that seen in the adult, i.e. an increase in the retinal input projecting to a given tectal site. This may be due to the desensitization of nicotinic receptors. Nicotine has also been demonstrated to have bidirectional effects on synaptic plasticity in the immature hippocampus [57].

Acetylcholine is supplied to the frog optic tectum only by exogenous sources with over 90% contributed by a single source, the nucleus isthmi [18,61,95]. Lesions of the nucleus isthmi result in scotomas or blind spots in the frog's visual field even though direct retinal ganglion cell input to the optic tectum remains intact [37]. This result implies that the nucleus isthmi has a facilitating effect