Nicotinic Acetylcholine Receptors in Sensory Cortex

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Acetylcholine release in sensory neocortex contributes to higher-order sensory function, in part by activating nicotinic acetylcholine receptors (nAChRs). Molecular studies have revealed a bewildering array of nAChR subtypes and cellular actions; however, there is some consensus emerging about the major nAChR subtypes and their functions in sensory cortex. This review first describes the systems-level effects of activating nAChRs in visual, somatosensory, and auditory cortex, and then describes, as far as possible, the underlying cellular and synaptic mechanisms. A related goal is to examine if sensory cortex can be considered a model system for cortex in general, because the use of sensory stimuli to activate neural circuits physiologically is helpful for understanding mechanisms of systems-level function and plasticity. A final goal is to highlight the emerging role of nAChRs in developing sensory cortex, and the adverse impact of early nicotine exposure on subsequent sensory–cognitive function.

Nicotinic acetylcholine receptors (nAChRs) contribute to sensory–cognitive functions, as demonstrated in numerous behavioral studies (Warburton 1992; Turchi et al. 1995; Rezvani et al. 2002). The contribution likely involves nAChRs located within sensory systems, including sensory cortex, that mediate the cholinergic role in attention and other cognitive functions[1] (Sarter et al. 2001). An understanding of the role of nAChRs in sensory cortex function requires integrating information on the different subtypes of nAChRs, how they respond to acetylcholine (ACh) or psychoactive drugs, where they are found (which areas and layers, on which cell types, and whether they are pre- or postsynaptic), and the consequences of their activation for the processing of sensory information in neural circuits. Although considerable information exists regarding the molecular biology, cellular physiology, and general distribution in the brain of nAChR subtypes (Jones et al. 1999; Dani 2001; Leonard and Bertrand 2001), complementary information on how nAChRs function within specific cortical circuits is needed to understand nicotinic functions in sensory cortex—or, for that matter, anywhere in the CNS (Alkondon and Albuquerque 2003; Clarke 2003; Metherate and Hsieh 2003).

The neuronal nAChR is a pentamer that can include a combination of α and β subunits as a heteromeric receptor, or five α subunits as a homomeric receptor (Dani 2001; Leonard and Bertrand 2001). Although there are genes for a large number of subunits ($\alpha 2$–10, $\beta 2$–4), most nAChRs in cortex are thought to exist as heteromers with $\alpha 4$ and $\beta 2$ subunits or as $\alpha 7$ homomers (note that this scenario is almost certainly an oversimplification). From a functional viewpoint, knowing the receptor composition is important because subunits contribute distinct functional characteristics, as shown by studying different subunit combinations in expression systems (Role and Berg 1996; Fenster et al. 1997). Notably, $\alpha 7$-containing receptors are known for rapid desensiti-

zation in the presence of agonist and high Ca^{2+} permeability[2] (Zhang et al. 1994; Castro and Albuquerque 1995), whereas $\alpha 4 \beta 2$-containing receptors have higher affinity to nicotine and slower rates of densensitization (Fenster et al. 1997).

There is remarkably little information on how nAChRs are engaged within cortical circuits, in part because synaptic actions of ACh at cortical nAChRs are difficult to demonstrate and study (in contrast, e.g., to ACh at the neuromuscular junction or glutamate in the cortex). The reasons for this difficulty lie partly in the nature of the cholinergic innervation of neocortex. The major source of cortical ACh is the nucleus basalis in the basal forebrain, whose cholinergic neurons are intermixed with noncholinergic neurons (some of which also project cortically), and whose cortical projection is diffuse (Rye et al. 1984; Dykes 1997). Such features make the cholinergic projection difficult to stimulate selectively. Also, cholinergic actions in the cortex appear to involve tonic release via "volume transmission," whereby ACh is released far from its postsynaptic targets (Umbriaco et al. 1994; but see Turrini et al. 2001). Although it may seem odd to have a transmitter system that incorporates, for example, tonic volume transmission with postsynaptic receptors that desensitize very rapidly, overcoming experimental design problems to be able to study such features will be key to understanding the role of nAChRs in cortical circuits.

Given the obstacles to studying synaptic actions at nAChRs, it is not surprising that most functional information has been obtained using receptor agonists such as nicotine. Although agonist use is common in receptor studies, it takes on special significance for nAChRs because nicotine is the main psychoactive agent in tobacco. Nicotine from cigarette smoke affects sensory perception and cognitive processes, and the effects of its use on brain function have been studied extensively (Warburton 1992; Dani and Heinemann 1996). Thus, nicotinic agonists are useful not only for studying the properties of nAChRs, but also for un-

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[1] ACh activates two broad classes of receptors, namely, nicotinic and muscarinic receptors. Whereas this review focuses on nicotinic receptors, many studies have established the importance of muscarinic receptors in modulating sensory cortex function and plasticity (for reviews, see Weinberger and Bakin 1998; Edeline 1999; Rasmusson 2000; Metherate and Hsieh 2003).

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[2] Permeability to Ca^{2+} is an important feature of some nAChRs, for example, presynaptic receptors whose activation results in increased neurotransmitter release (Wonnacott 1997), and $\alpha 7$ receptors may be even more permeable to Ca^{2+} than NMDA receptors (Seguela et al. 1993). Also, nAChR-associated increases in intracellular Ca^{2+} levels can result from the activation of voltage-dependent Ca^{2+} channels or release from intracellular stores (Zhang et al. 1994; Sharma and Vijayaraghavan 2003).

derstanding how tobacco use—systemically administered nicotine—affects neuronal circuitry and function.

Finally, there is a growing awareness that nAChRs may have distinct functions at different stages of life. In particular, several recent studies have found distinct and possibly unique mechanisms at work during brain development (Role and Berg 1996; Broide and Leslie 1999), including the development of sensory cortex (Metherate and Hsieh 2003). Given these findings, it is not surprising that smoking by pregnant women can impact fetal brain development (a particularly tragic consequence of nicotine addiction is that many women do not quit smoking during pregnancy; Oncken and Kranzler 2003). The effects of prenatal nicotine exposure can be detected even years later in the children of smokers (Ernst et al. 2001; Fried and Watkinson 2001).

Focus of This Review

The goal of this review is to highlight the extent to which nAChRs regulate sensory information processing, and to promote an understanding of the underlying mechanisms. The review focuses on the cellular and system-level effects of activating nAChRs in sensory neocortex (visual, somatosensory, and auditory cortex). Molecular and behavioral studies are not emphasized, although the effects of nicotine at specific nAChR subtypes, and on sensory–cognitive function, are noted. A secondary goal is to examine the extent to which sensory cortex can be considered a model system for cortex in general. Sensory systems can serve as useful models because physiological activation of neural circuits is possible (using sensory stimuli), thus enabling studies that integrate information across levels from the molecular to psychophysics. To that end, the review notes relevant differences and similarities with nonsensory cortical regions, and directs the interested reader to the literature for further details. A final goal of the review is to highlight the emerging role of nAChRs in developing sensory cortex, and the impact of early nicotine exposure on subsequent sensory–cognitive function.

Cortical nAChRs Regulate Responses to Sensory Stimuli

A simple observation to begin with is that administering nicotine systemically in humans, or smoking tobacco[3], alters physiological measures of sensory responsiveness that involve sensory cortex, for example, sensory-evoked neural responses recorded from the scalp. In smokers, smoking increased the amplitude of long-latency visual (flash)-evoked potentials, whereas abstinence from smoking for many hours reduced the evoked potential amplitude (Hall et al. 1973; Friedman and Meares 1980). Similarly, in the auditory system, smoking increased the amplitude and reduced the peak latency of middle latency (midbrain and forebrain) components of an auditory (click)-evoked potential relative to the response obtained following a period of abstinence, or relative to the response in nonsmokers (Kishimoto and Domino 1998; but see Friedman and Meares 1980). Earlier latency (brainstem) components of the auditory-evoked potential appeared unaffected by smoking or abstinence. Enhancement of visual-evoked potentials was seen after smoking cigarettes containing 1.34 mg of nicotine relative to cigarettes containing 0.14 mg (considered a pharmacologically ineffective dose), implicating nicotine or its metabolites in the effect (Woodson et al. 1982).

[3]Smoking tobacco increases levels of nicotine in the blood and brain (Isaac and Rand 1972; Henningfield et al. 1993). Although nicotine is considered the main psychoactive ingredient in tobacco, note that nicotine metabolites exert effects on the brain, as do other components of tobacco smoke (e.g., carbon monoxide), and that some consequences of nicotine administration may be indirect, for example, resulting from changes in brain blood flow or nicotine-induced release of neuromodulators or hormones (Benowitz 1996; Crooks and Dwoskin 1997; Domino et al. 2000; Ernst et al. 2001; Oncken and Kranzler 2003).

In a more direct examination of nicotine's effects on auditory processing, systemic nicotine delivered to nonsmokers transdermally, via a nicotine "patch," did not affect a measure of peripheral auditory function (otoacoustic emissions in the cochlea), but did affect CNS responses to auditory stimuli (Harkrider and Champlin 2001a,b; Harkrider et al. 2001). The study was conducted on nonsmokers to avoid complications arising from the effects of chronic nicotine exposure, but consequently was limited to a low-dose patch because of unpleasant side effects (dizziness, nausea; the patch was designed to release 7 mg/24 h and remained in place for 4 h). The patch produced modest changes (both increases and decreases) in latency and amplitude of specific evoked potential components associated with auditory nuclei throughout the auditory pathway, including increased amplitude and decreased latency of long-latency (forebrain) potentials.

Examining nicotine's effects in animals enables more precise localization of recorded signals. In awake restrained cats, systemic nicotine (25–100 μg/kg, i.p.) increased the peak amplitude of the click-evoked potential recorded from the surface of auditory cortex (Guha and Pradhan 1976). A lower dose (12.5 μg/kg) transiently reduced the evoked response. In the anesthetized rat, similar systemic doses of nicotine (25–100 μg/kg, i.p.) appeared not to affect the click-evoked potential recorded from the surface of auditory cortex (Bhargava et al. 1978). However, a more recent study found that a higher dose (0.7 mg/kg, s.c.) enhanced the magnitude and reduced the latency of pure tone-evoked field potentials recorded in layer 4 of rat auditory cortex (Liang and Metherate 2003). In rat visual cortex, nicotine (0.35 mg/kg, i.p.) reduced a longer-latency component (N41) of the flash-evoked epidural potential (Bringmann 1994).

These studies demonstrate that systemically administered nicotine affects sensory processing, and that changes may occur at multiple levels in each sensory pathway. This is consistent with known cholinergic anatomy; for example, nicotine's effects on distinct components of the auditory-evoked response is consistent with the widespread distribution of nAChRs in the auditory pathway (Morley and Happe 2000). Another important point to remember is that systemic nicotine likely activates cortically projecting neuromodulatory systems (e.g., the "reticular activating system" and nucleus basalis) that contribute to the modification of sensory-evoked cortical responses (Shute and Lewis 1967; Guha and Pradhan 1976; Lewandowski et al. 1993; Metherate and Ashe 1993; Azam et al. 2003). Obviously, changes in cortical responses could incorporate nicotinic actions at several subcortical levels.

The involvement of cortical nAChRs can be demonstrated by direct manipulation within the cortex. Iontophoretic application of the nAChR antagonist mecamylamine (100 μM pipette solution) in the middle layers of cat visual cortex reduced single unit responses to visual stimuli (moving bars; Parkinson et al. 1988). Similarly, in rat auditory cortex, microinjection of 10 μM mecamylamine into the middle layers reduced tone-evoked potentials in layer 4 (Liang and Metherate 2003). Both studies implicate cortical nAChRs in the regulation of sensory responses. Importantly, because reduction of evoked responses occurred during delivery of antagonist alone (i.e., in the absence of exogenous nicotine), the findings also imply that tonic release of endogenous ACh acts at nAChRs to regulate sensory responses.

Complementary results have been obtained from rat somatosensory cortex, where deflection of a whisker evokes neural activity in a cortical area centered over the appropriate whisker representation ("barrel"). Nicotine (100 μM) applied to the cortical surface increased the peak amplitude and area of the whisker representation, as assessed by intrinsic signal imaging (Penschuck et al. 2002). Control studies showed that the imaging

technique preferentially samples activity in the upper and middle cortical layers, and the method of agonist application also preferentially affects the same layers. In another study, intracortical microdialysis of nicotine (1 mM delivered to the microdialysis probe; estimated <10% concentration in adjacent tissue) enhanced the whisker-evoked field potential recorded in layer 4 adjacent to the microdialysis probe, but did not affect the intracortical response to electrical stimulation of nearby cortex (Oldford and Castro-Alamancos 2003). Taken together, these studies demonstrate that nAChRs located in the primary auditory, visual, and somatosensory cortices contribute to the enhancement of sensory responses.[4]

Cellular Bases of Nicotinic Regulation of Sensory Cortex

Early in vivo studies of cholinergic drugs applied iontophoretically to single neurons in cat and rat sensory cortex noted infrequent increases in spontaneous activity with nicotine, and only moderate effectiveness of neuromuscular junction antagonists such as curare (Krnjevic and Phillis 1963; Stone 1972; Lamour et al. 1982). In general, these studies implied a far greater role for muscarinic receptors in mediating effects of ACh. The lack of prominence given to nicotinic actions may have resulted from unrecognized features of neuronal nAChRs such as rapid receptor desensitization, preferential location on interneurons and presynaptic terminals, and pharmacology unlike that of muscle nAChRs.

More recent anatomical studies reinforce the likelihood of nicotinic actions in sensory cortex, in particular providing evidence that nAChRs regulate thalamocortical transmission (Clarke 2003). Studies in rat brain show dense, high-affinity [3H]nicotine binding (hereafter referred to as nicotine binding) through much of the neocortex, including sensory cortex, mostly in cortical layers 3 and 4 (but also in layers 1 and 6), where thalamocortical inputs terminate (Clarke et al. 1984, 1985; London et al. 1985). (Notably, α-bungarotoxin [αBTX] binding sites are not in the middle layers but are deeper in layer 6 instead.) In cat visual cortex, similar dense nicotine binding is found in layers 3/4, with a dramatic drop in density at borders of visual cortex (decreased density at the area 17/18 border, and again at the area 18/19 border; Prusky et al. 1987; Parkinson et al. 1988). These authors tested the notion that nAChRs are associated with thalamocortical fibers by surgically undercutting the cortex or by making electrolytic lesions of the lateral geniculate nucleus (LGN). These manipulations reduced the dense layer 4 binding. In contrast, excitotoxic lesions of visual cortex, which destroyed neurons within the cortex, but not afferent fibers, did not significantly affect the layer 4 band. These data support the idea that nAChRs are found on afferent terminals, in particular those of thalamocortical projections. Note that the incomplete, although substantial, loss of cortical nicotine binding even after extensive thalamic lesions, along with apparently complete loss of binding after cortical undercut, indicates the existence of presynaptic nAChRs associated with other afferent systems.

In similar experiments in the rat, excitotoxic or electrolytic thalamic lesions centered on the ventrobasal thalamus (but extending beyond its borders) that reduced layer 4 nicotine binding in sensory-motor cortex did not affect labeled muscarinic receptors, whereas excitotoxic lesions of the cortex reduced muscarinic, but not nicotinic, labeling (Sahin et al. 1992). The authors

concluded that nAChRs are located on thalamocortical terminals, whereas muscarinic receptors are located postsynaptically on cortical neurons. Subsequent studies have found similar results in rat auditory and visual systems (Lavine et al. 1997): excitotoxic thalamic lesions centered on the medial geniculate (MG) or LGN reduced nicotine binding in layer 4 of auditory cortex or visual cortex, respectively. Conversely, excitotoxic lesions of temporal/auditory cortex did not affect nicotine binding, despite loss of cortical neurons. Importantly, the authors note that subsequent to the earlier studies, it had been demonstrated that high-affinity nicotine-binding sites reflect nAChRs containing α4 and β2 subunits (whereas low-affinity nicotine- or αBTX-binding sites are thought to reflect α7 receptors; Couturier et al. 1990; Seguela et al. 1993). Thus, a contribution to the nicotine-induced increase in sensory cortex responsiveness ("Cortical nAChRs Regulate Responses to Sensory Stimuli" section above) may depend on presynaptic, α4β2-containing nAChRs that regulate thalamocortical transmission.

The idea that presynaptic nAChRs regulate thalamocortical transmission must be tested in physiological experiments. Cellular and synaptic physiology in sensory cortex is examined mostly in brain slices from young rodents[5], and this particular issue is best addressed using a thalamocortical slice preparation (Agmon and Connors 1991; Cruikshank et al. 2002). In the only direct test to date, 1 μM bath-applied nicotine enhanced thalamic-evoked glutamatergic responses, but did not affect intracortically evoked responses, in layer 4 of the somatosensory thalamocortical slice obtained from 2- to 3-week-old rats or mice (Gil et al. 1997). Curiously, the effect in rat slices was blocked by 0.1–0.5 μM methyllycaconitine (MLA; reportedly selective for α7 nAChRs) or by 10 μM mecamylamine (reportedly nonselective among nAChR subtypes); however, in mouse slices the effect was blocked by mecamylamine but not MLA. The authors concluded that the nicotine effect was due to α7 receptors in rats, and non-α7 receptors in mice. These results imply an interesting species difference; however, it should be noted that the MLA dose used may block non-α7 receptors, and the mecamylamine dose may preferentially block non-α7 receptors (e.g., Raggenbass and Bertrand 2002). Also, the authors did not explicitly consider the rapid changes in nAChR expression that occur during the first three postnatal weeks in sensory cortex and thalamus (Fuchs 1989; Bina et al. 1995; Broide et al. 1995, 1996). These changes are detailed below ("nAChRs and Sensory Cortex Development"), and it remains a possibility that different nAChR subtypes regulate thalamocortical transmission at different ages (e.g., Fig. 1). Nonetheless, the results support the general hypothesis that presynaptic nAChRs regulate thalamocortical transmission in sensory cortex.

In vitro studies also have demonstrated the cellular basis of rapid excitation of postsynaptic neurons that is mediated by nAChRs, and it now appears that in sensory cortex, such actions are most prominent in interneurons (but see "Synaptic Responses and Other Evidence for Endogenous Activation of nAChRs" below). This may have contributed to the early findings of infrequent nicotine-mediated excitation in vivo, because it is difficult to record from interneurons in vivo. In the last decade, however, studies have been able to target sparse or small neurons in brain slices because of technical advances that enable whole-cell

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[4]Another form of sensory processing, "sensory gating," involves α7 nAChR-mediated regulation of auditory processing in the hippocampus (Adler et al. 1998; Freedman et al. 2000). A sensory gating deficit has been observed in schizophrenics, and has been attributed to a genetic defect underlying impaired α7 nAChR function in hippocampal interneurons. Notably, this and other symptoms are transiently reversed by nicotine, a finding that may explain the very high rates (~90%) of smoking among schizophrenics.

[5]Note that the anatomical work cited above derives from adult rats and cats, whereas most slice work is done in 2- to 3-week-old rodents (it is widely known among slice physiologists, though rarely mentioned in print, that whole-cell recordings become considerably more difficult in animals older than ~3 wk). Thus, physiological results from slices may unwittingly reflect processes that occur only during postnatal development; such changes in nAChR function have become more apparent recently (see "nAChRs and Sensory Cortex Development" below).
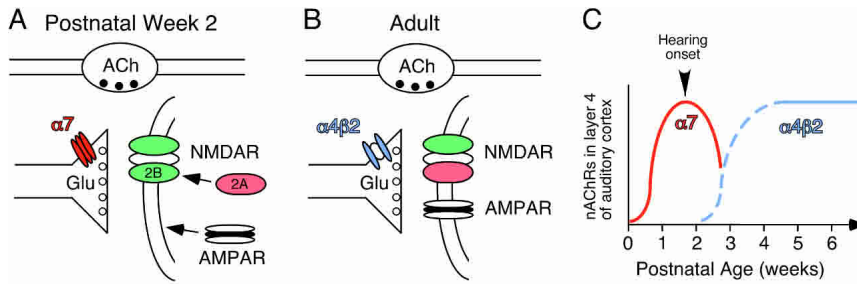
Figure 1 Hypothesized synaptic arrangement (*A,B*) and developmental time course (*C*) of nAChR-mediated regulation of glutamate synapses in layer 4 of rat sensory cortex (including relation to onset of hearing for auditory cortex, *C*). For simplicity, the figure deals only with presynaptic nAChRs in cortical layer 4 (see text for discussion of postsynaptic nAChRs in layer 4 and nAChRs in other layers). (*A*) During early postnatal development, presynaptic α7-containing nAChRs regulate glutamate release at pure-NMDAR synapses. (Other synapses, not shown, have both AMPARs and NMDARs but no presynaptic α7 receptors.) When ACh is released from axons originating in the nucleus basalis, nAChR stimulation may contribute to activity-dependent insertion of AMPARs into the plasma membrane and NR2A subunits into NMDARs (2A and 2B refer to NR2A and NR2B subunits of NMDAR). (*B*) In the mature sensory cortex, α4β2-containing nAChRs regulate glutamate release at thalamocortical synapses; such receptors may be presynaptic (as shown) or preterminal (Lambe et al. 2003). (*C*) Developmental time course of nAChR expression in layer 4 of auditory cortex, and relation to onset of hearing during postnatal Week 2. The degree to which α7 nAChRs are associated with thalamocortical synapses, as opposed to other glutamatergic synapses, is uncertain. In contrast, α4β2 nAChRs likely regulate thalamocortical synapses in adults, but their level of expression during early development remains unclear (dotted line). Note that these events are hypothesized to occur postnatally in the rat but prenatally in the human (see text for details).

(patch) recordings from visually identified neurons (Blanton et al. 1989; Dodt and Zieglgansberger 1990). The following studies all have exploited these newer techniques.

In visual cortex slices from ~2-week-old rats, ACh (5 mM, micropressure ejection) strongly and rapidly depolarized low-threshold spiking (LTS) interneurons in layer 5, an effect that was blocked by the nicotinic antagonist hexamethonium (5 mM, micropressure ejection; Xiang et al. 1998). These GABAergic interneurons preferentially project to the upper cortical layers, and would be expected to inhibit pyramidal neurons within the same cortical "column" when excited. Interneurons in layer 1 have been studied in slices from the somatosensory cortex of 2- to 3-week-old rats (Christophe et al. 2002). Layer 1 has a particularly rich innervation of cholinergic axons and putative synapses (Mechawar et al. 2000). Micropressure-ejected nicotinic agonists excited nearly all layer 1 interneurons (97 of 101); the agonist-induced responses had fast and slow response components that showed pharmacological sensitivity consistent with α7 and non-α7 receptors, respectively. (Some layer 1 interneurons excited by nicotine also are known to contain the peptides VIP and/or CCK, in addition to GABA, and receive synaptic inputs mediated by serotonin; Ferezou et al. 2002.) The authors then performed single-cell RT-PCR to show that the cells contained mRNA for α4, α7, and β2 subunits, implying that each interneuron's mixed nAChR population included α7 homomers and α4β2 heteromers. Finally, they demonstrated that nicotinic agonist application to layer 1 resulted in IPSPs recorded in many layer 2/3 interneurons, though never in layer 2/3 pyramidal neurons, indicating that nicotinic excitation of layer 1 disinhibits deeper layers via inhibition of layer 2/3 interneurons. Together, these studies indicate robust nicotinic excitation of several types of GABAergic interneuron.

These studies are somewhat at odds with experiments showing nicotinic synaptic transmission in pyramidal neurons in ferret visual cortex (Roerig et al. 1997; discussed below), and a recent ultrastructural study of somatosensory cortex in 1-week-old and adult rats (Levy and Aoki 2002). The latter study demonstrated antibody label for α7 nAChRs associated with >70% of glutamate synapses (mostly postsynaptic, but also some presyn-

aptic label) across all layers. Because label was found mostly at axospinous synapses, which likely indicate synapses onto pyramidal neurons rather than (aspinous) interneurons, it is hard to integrate these data with the above physiological data showing excitation of interneurons, but not pyramidal neurons. It may be important that the physiological studies described above did not, for the most part, examine nicotinic regulation of glutamatergic transmission; further, the authors suggest that some α7-mediated functions are not easily detected physiologically (Levy and Aoki 2002).

Overall, the bulk of anatomical and physiological studies to date support two main functions of nAChRs in sensory cortex: presynaptic regulation of thalamocortical (glutamatergic) transmission and postsynaptic excitation of a subset of GABAergic interneurons.

Related Findings in Nonsensory Cortex

This and subsequent sections with the same subtitle compare actions of nAChRs in sensory to nonsensory cortex, with the emphasis on highlighting broad similarities and differences. Additionally, some relevant findings from nonsensory cortex are mentioned even if comparison studies in sensory cortex have not yet been performed.

Several studies have examined nicotinic actions in prefrontal cortex, in part because of the putative role of nAChRs in cognitive/attentional processes mediated by prefrontal cortex (Granon et al. 1995). Studies analogous to those described above for sensory cortex make the case that nAChRs regulate thalamocortical afferents from the mediodorsal thalamic nucleus (MD) to prefrontal cortex (Vidal and Changeux 1989, 1993; Lavine et al. 1997; Gioanni et al. 1999). In anatomical experiments, excitotoxic MD lesions reduced nicotine binding preferentially in prefrontal cortex. In physiological experiments, nicotinic agonists facilitated the glutamatergic response to stimulation of MD (in vivo) or afferents within the cortical thalamorecipient layer (in vitro). In microdialysis experiments, nicotine increased cortical glutamate release in vivo. Both functional assays (electrophysiology and microdialysis) revealed pharmacological sensitivity that implicates α4β2 subunits. In a novel in vitro approach, nicotinic agonists were found to increase the frequency of spontaneous excitatory postsynaptic currents (EPSCs) in prefrontal neurons that receive thalamocortical inputs; this apparent presynaptic (and in fact, the authors conclude, given that tetrodotoxin blocks the effect, "preterminal") effect did not occur in slices from rats with thalamic lesions, nor in transgenic mice lacking β2 subunits (Lambe et al. 2003). Together, these studies provide good evidence that α4β2 nAChRs regulate thalamocortical transmission in prefrontal cortex, as in mature sensory cortex.

Data from hippocampal neurons, in brain slices or in cell culture, also provide evidence for presynaptic actions of nAChRs, but with a different pharmacological profile. Nicotinic receptors have been shown to enhance glutamate release via increased Ca^{2+} influx into presynaptic terminals; however, the pharmacological data indicate α7-containing nAChRs (Gray et al. 1996). Enhanced glutamate release can be maintained in the presence of low concentrations of agonist (e.g., 0.5 μM nicotine), presumably reflecting the involvement of nAChR-mediated Ca^{2+} influx, and, possibly, reduced receptor desensitization with low agonist concentrations (Shao and Yakel 2000). Following strong agonist

stimulation, enhanced glutamate release can outlast the presence of agonist for minutes (Radcliffe and Dani 1998). Nicotinic increases in the frequency of spontaneous GABAergic currents also can depend on α7 receptors (Radcliffe et al. 1999; Alkondon and Albuquerque 2001), and recent data also have implicated α3β4-containing receptors in the control of glutamate release (Alkondon et al. 2003). Thus, the predominant pharmacology of presynaptic nAChR actions in hippocampus may differ from that of prefrontal or sensory neocortex.

Finally, as with sensory cortex, nAChR-mediated postsynaptic excitation in other cortical regions often occurs in interneurons. In brain slices from motor cortex, parietal association cortex, and hippocampus, nicotinic agonists exert negligible direct actions on pyramidal/principal neurons (however, see Ji et al. 2001) but strongly excite GABAergic and other local circuit neurons via non-α7 and, especially, α7 nAChRs; this action could, in turn, strongly inhibit pyramidal neurons (Jones and Yakel 1997; Frazier et al. 1998b, 2003; Porter et al. 1999; Alkondon et al. 2000; Ji and Dani 2000; Ji et al. 2001; Christophe et al. 2002).

Synaptic Responses and Other Evidence for Endogenous Activation of nAChRs

Despite abundant evidence for functional nAChRs in cortex, remarkably few studies have reported direct evidence for nicotinic synaptic transmission. In particular, only one study to date has recorded synaptic currents mediated by nAChRs in sensory cortex. In visual cortex brain slices taken from ferrets over a wide age range (2 to 10 weeks old), both spontaneous and stimulus-evoked EPSCs occurred in pyramidal neurons found in layers 2–3 and 5–6, and in interneurons (both spiny and aspiny) found in layer 4 (Roerig et al. 1997). The EPSCs were blocked by 100 µM dihydo-β-erythroidine (DHβE), but not by 200 nM αBTX, implicating non-α7 receptors. Two findings stand out, especially in light of the studies reviewed above. First, both spontaneous and evoked EPSCs were of relatively small amplitude (e.g., 5–60 pA); however, the authors note that seemingly weak synaptic currents may carry additional weight given the Ca^{2+} permeability of nAChRs (although high Ca^{2+} permeability is more prominently a feature of α7 nAChRs). Second, nicotinic EPSCs were observed commonly in pyramidal neurons, whereas agonist-mediated excitation of pyramidal neurons is rare in other studies. Given the number of differences among the studies (e.g., species), future experiments must be designed carefully to resolve the seeming discrepancy.

Indirect evidence for activation of nAChRs by endogenous transmitter in sensory cortex also exists, and is consistent with the hypothesized role of nAChRs to regulate thalamocortical afferents. The evidence has been described in previous sections, and includes sensory-evoked responses being reduced by the antagonist mecamylamine delivered alone (Parkinson et al. 1988; Liang and Metherate 2003), or being enhanced by the delivery of anticholinesterase (or nicotine; Oldford and Castro-Alamancos 2003). Obviously, the success of this approach requires ongoing release of ACh in cortex, even in anesthetized animals, and indeed, this has been demonstrated by direct measurements (Celesia and Jasper 1966; Phillis 1968; Rasmusson et al. 1994). (In a related vein, it should be noted that choline, a precursor to ACh and product of ACh hydrolysis, is a selective agonist at α7 nAChRs; Alkondon et al. 1997.) The tonic release of cortical ACh in virtually all conditions (and even in brain slices; Metherate and Ashe 1995)—albeit at greater or lesser levels in different states of arousal—is an oft-forgotten but important feature that must be kept in mind when designing and interpreting cholinergic studies.

Related Findings in Nonsensory Cortex

Nicotinic EPSCs also have been observed in slices from hippocampus (Alkondon et al. 1998; Frazier et al. 1998a; Hefft et al. 1999) and frontal cortex (Chu et al. 2000). Synaptic currents were observed in both interneurons and pyramidal neurons (again, in contrast to agonist studies), were of small amplitude (~2%–10% of the total synaptic response), show reversal potentials near 0 mV, and often show strong dependence on α7 receptors. Most studies assume that the presynaptic axons are cholinergic extrinsic inputs to the slice that remain functional even when severed (i.e., they support action potentials and release transmitter). Interestingly, however, one study noted that because similar responses were seen in organotypic slice culture as in acute slices, it seems possible that cholinergic neurons intrinsic to the slice—rather than severed axons that would not survive in a slice culture—mediate the synaptic response (Hefft et al. 1999). Putative cholinergic neurons are intrinsic to the neocortex, as well, but have been largely ignored in physiological studies. Finally, one study has provided evidence that stimulation of cholinergic pathways to the hippocampus acts via presynaptic α7 receptors to produce long-lasting increases in the probability of glutamate release (Maggi et al. 2003). Thus, endogenous ACh has been shown to act at both pre- and postsynaptic nAChRs in nonsensory cortex.

nAChRs and Sensory Cortex Development

A wealth of anatomical evidence accumulated over more than two decades points to a transient cholinergic function that occurs specifically in sensory neocortex during development. Initial studies focused on the distribution of staining for acetylcholinesterase (AChE), the cholinergic hydrolytic enzyme (Kristt 1979a,b). These studies reported a dense AChE staining primarily in layer 4 (but also in layers 1 and 6) of rat somatosensory cortex. The staining appeared shortly after birth, peaked in density over 1–2 wk, and was not apparent after postnatal day (P) 21 (although a different AChE laminar pattern, less dense, remains into adulthood). At its peak, the AChE density showed clearly outlined barrels in tangential sections through layer 4. The areal, laminar, and temporal development of the AChE staining corresponded to that of thalamocortical afferents that reach layer 4 shortly after birth and proliferate over the subsequent 1–2 wk (Catalano et al. 1991, 1996), leading to the proposal that the AChE marked ingrowing thalamocortical afferents. In support of this idea, cortical undercut reduced the AChE stain in layer 4 (Kristt 1979a); however, it is not clear why the dense layer 4 AChE staining disappears after the third postnatal week.

These initial findings subsequently were extended to the rat visual and auditory cortices (Robertson et al. 1985, 1991; Prusky et al. 1988). In both cortices, dense layer 4 AChE staining begins to appear in postnatal Week 1, peaks in density during Week 2, and is reduced to low (adult) levels after Week 3. The AChE in layer 4 of visual or auditory cortex was coextensive with transneuronal labeling of layer 4 with horseradish peroxidase (HRP) deposited in the eye (Kageyama et al. 1990) or inferior colliculus (Robertson et al. 1991), respectively, confirming the correlation with thalamocortical arbors. Similarly, lesion of the auditory pathway (medial geniculate or inferior colliculus), or enucleation of the eye, reduced AChE levels in layer 4 but not in other layers of auditory or visual cortex. Conversely, basal forebrain lesions that disrupted the cholinergic projection to the cortex reduced the AChE stain outside of, but not within, layer 4. It seems clear that dense AChE staining is associated with thalamocortical afferents during postnatal development of sensory cortex.

Other studies have shown that nicotine binding in layer 4 of sensory cortex also appears during postnatal development, but

the degree to which this mirrors the transient AChE staining is not clear. Studies in rat visual cortex showed that layer 4 nicotine binding transiently increased in Weeks 2–3, and then either decreased in Week 4 to remain at low levels into adulthood (Kumar and Schliebs 1992) or returned to high levels in adulthood (Prusky et al. 1988). In the latter study, the adult layer 4 binding pattern extended throughout much of neocortex—that is, corresponding to the putative presynaptic α4β2 nAChRs associated with thalamocortical terminals (described in "Cellular Bases of Nicotinic Regulation of Sensory Cortex" above)—whereas the Week 2 pattern was restricted to visual cortex (and, weakly, in auditory cortex; Prusky et al. 1988). Other studies indicate that cortical nicotine binding peaked later (Weeks 3–4 in the rat) and remained strong into adulthood (Sershen et al. 1982; Yamada et al. 1986; Slotkin et al. 1987; Naeff et al. 1992; Aubert et al. 1996). However, these latter studies did not always distinguish between sensory and nonsensory cortex, and may not have detected an early, transient increase in nicotine binding if it occurred only in sensory cortex. Thus, the nicotine binding in adult sensory cortex (presumed α4β2 nAChRs) is apparent late in postnatal development, but its relationship to nicotine binding and transient AChE staining earlier in development remains unclear.

In contrast, additional studies point to a transient role for α7 nAChRs in sensory cortex development, one with a developmental time course that more closely parallels that of the AChE staining. In rat cortex, labeled αBTX binding appears in each sensory neocortex starting at P0, peaks around P10, at which point it delineates each primary sensory cortex, and then fades to lower (adult) levels by P20 (uniform low level distribution across sensory and nonsensory cortex; Fuchs 1989). At its peak, the laminar pattern shows two regions of high density, in layer 4 and layers 5/6, whereas only weaker label in the deeper layers persists in the adult. More recent studies in the rat have shown a close developmental correlation of transient αBTX binding, AChE staining, and expression of α7 mRNA in each sensory neocortex and the corresponding thalamic relay nuclei[6] (Broide et al. 1995, 1996). In somatosensory cortex, all three measures coincide in layer 4, but only αBTX binding and α7 mRNA expression occur in layer 6. Importantly, thalamic lesions were found to reduce cortical levels of α7 mRNA within hours, and before AChE staining decreased; because mRNA is expressed in cortical neurons, whereas AChE marks thalamocortical fibers, the authors suggest that some, at least, of the cortical α7 nAChR expression is postsynaptic and yet regulated by thalamocortical inputs. However, additional evidence—including a more discrete cortical label pattern for αBTX than for mRNA, and thalamic expression of α7 mRNA—is consistent with a presynaptic function for α7 nAChRs in thalamocortical transmission (Broide et al. 1996). Thus, both pre- and postsynaptic α7 nAChRs may have transient roles in sensory cortex development.

Several studies support the relevance of the findings in these animal models to human sensory cortex development, but show that postnatal development in the rodent more closely resembles prenatal (third trimester) human development. In the developing human auditory system, AChE staining marks thalamocortical afferents as they emerge from the diencephalon and grow toward the auditory cortex (Krmpotic-Nemanic et al. 1983). Early in the third trimester (~Week 28 of gestation), the AChE forms densely stained zones in layer 4 of auditory cortex, delineating it from the surrounding temporal cortex (Krmpotic-Nemanic et al.

1980). Notably, a similar species difference applies to the onset of sensory function: The rat begins to hear in postnatal Week 2 (Jewett and Romano 1972; Iwasa and Potsic 1982), whereas human hearing begins early in the third trimester (Moore 2002). Thus, auditory cortex development during postnatal Weeks 1–3 in the rat is similar to human third trimester development in terms of (1) growth and proliferation of thalamocortical inputs into layer 4, (2) dense AChE staining in layer 4, and (3) the onset of hearing. Some possible functional implications of this convergence of events are discussed below.

Despite the large number of anatomical reports suggestive of a transient cholinergic function in developing sensory cortex, a physiological examination was undertaken only recently.[7] In a brain slice study of rat auditory cortex, nicotine (0.5–25 μM) was pressure-ejected onto the dendrites of pyramidal neurons in layers 3–4 and found to modify their responses to afferent glutamatergic stimulation (Aramakis and Metherate 1998). Nicotine selectively enhanced the late, N-methyl-D-aspartate receptor (NMDAR) component of the EPSP without affecting the early, α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid receptor (AMPAR) component. Because MLA (5 nM) blocked the effect, as did preceding bath application of nicotine (0.3–10 μM for several minutes), and because nicotine did not enhance responses to iontophoretically applied glutamate, the effect was considered caused by rapidly desensitizing, presynaptic α7 nAChRs located on glutamatergic terminals[8] (Fig. 1A). Developmentally, the effect occurred most frequently (~90% of neurons tested) early in Week 2 in brains that had visible AChE staining in auditory cortex, and rarely (~6%) after the middle of Week 3 when the AChE staining had disappeared. Although the nicotinic enhancement of the NMDAR EPSP was more frequent before P12, the magnitude of the enhancement in individual neurons was significantly greater after P12 (Metherate and Hsieh 2003), a transition that may be related to the onset of hearing (Fig. 1C). (In a related note, it has been shown that the frequency of spontaneous EPSCs mediated by nAChRs in ferret visual cortex increases dramatically at the time of eye opening; Roerig et al. 1997).

To explain how presynaptic α7 receptors could selectively enhance postsynaptic responses mediated by NMDARs, but not AMPARs, it was proposed that glutamate synapses regulated by presynaptic nAChRs had only NMDARs postsynaptically ("pure-NMDAR" synapses; Fig. 1A), whereas other glutamate synapses had AMPARs (and/or NMDARs) postsynaptically but no presynaptic nAChRs; Aramakis and Metherate 1998; Metherate and Hsieh 2003). Pure-NMDAR synapses, often called silent synapses, occur in developing sensory cortex and are thought to be converted to mature synapses with activity (depolarization)-dependent insertion of AMPARs (Isaac et al. 1997; Rumpel et al. 1998). We speculate that release of ACh in auditory cortex, for

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[6]Transient appearance of α7 mRNA and αBTX binding also has been demonstrated in mouse somatosensory cortex, with a similar developmental time course and laminar distribution (Bina et al. 1995). However, these cortical markers are not accompanied by a corresponding expression in the thalamus, indicating a possible species difference.

[7]As mentioned above, most physiological studies on brain slices use tissue from young rodents (2 to 3 weeks old) for ease of recording. Although this is a relevant developmental period for the issues being considered here, the in vitro studies of nAChRs typically are not explicitly developmental, that is, the data are grouped together rather than split by age, and they bear unknown relationships to the age-related changes in cholinergic markers. Most of the results have been discussed above, and will not be repeated here unless clearly relevant to development.

[8]In most neurons, nicotine applied by itself did not produce a postsynaptic response, but instead modified the response to afferent stimulation (Aramakis and Metherate 1998). However, in a minority (<20%) of neurons, the first application of nicotine by itself produced a rapid, robust postsynaptic depolarization. This effect was difficult to study, because it required many minutes to recover from presumed nAChR desensitization, in contrast to the nicotinic enhancement of EPSPs, which recovered within seconds. Thus, the nature of the direct nicotine effect is unknown, but may involve postsynaptic nAChRs for which anatomical evidence was described above (Broide et al. 1996; Levy and Aoki 2002).

example, during attention to behaviorally relevant sounds, may increase glutamate release at active synapses and facilitate their conversion to mature synapses with AMPARs (Fig. 1A). Such maturation would be expected to result in the loss of presynaptic α7 nAChRs (because nicotine did not enhance release at synapses containing AMPARs during development), and possibly, the eventual appearance of presynaptic α4β2 nAChRs in the adult (Fig. 1B,C). Thus, according to this hypothesis, α7 nAChR-mediated regulation of NMDAR synapses would be critical to experience-dependant maturation of cortical circuitry. It is relevant to note that α7 receptors have been implicated in several processes involving synapse development (Role and Berg 1996; Broide and Leslie 1999).

Related Findings in Nonsensory Cortex

A study mentioned in the previous section (Maggi et al. 2003) describes presynaptic α7 receptors in the neonatal hippocampus that, when activated, convert "silent" synapses to more mature synapses. However, the mechanism is different from that proposed here for auditory cortex, in that the synapses are presynaptically silent—insufficient glutamate is released to activate postsynaptic AMPARs—until α7 receptor stimulation results in a long-lasting increase in the probability of release. Also, interactions involving NMDARs and α7 nAChRs have been demonstrated in embryonic cortical neurons (Jensen et al. 1997) and hippocampal interneurons (Alkondon et al. 2003), but these do not seem closely related to interactions observed in sensory cortex.

Does the Transient, α7 nAChR-Mediated Regulation of Auditory Cortex Define a Critical Period?

A large body of evidence indicates that cholinergic and glutamatergic processes may contribute to postnatal critical periods initiated by the onset of sensory function, although most studies have focused on muscarinic ACh receptors or NMDARs (Bear and Singer 1986; Hohmann and Berger-Sweeney 1998; Fox et al. 1999; Yuste and Sur 1999). The studies reviewed here raise another possibility, one involving nAChRs and NMDARs. In the rat, the onset of hearing in Week 2 occurs at the height of α7-receptor-mediated regulation of NMDAR synapses in auditory cortex (Fig. 1C). Thus, this regulation may contribute to experience-dependent synaptogenesis and neural circuit formation. A clear implication of this hypothesis is that manipulating nAChR function should also affect the development of glutamate synapses and sensory function. To test this, rat pups were treated with chronic nicotine exposure (CNE; 0.35–0.7 mg/kg nicotine s.c. twice daily for 5–9 d; Aramakis et al. 2000). CNE during Week 2—but not during Weeks 1 or 4—altered glutamate synapse development dramatically: EPSPs after Week 2 CNE had longer durations and unusual, small fluctuations that may reflect altered mechanisms of release or hyperexcitable synaptic circuitry. Consistent with the hypothesized location of nAChRs at pure-NMDAR synapses, CNE altered only the NMDAR component of EPSPs—roughly doubling the magnitude of this component—but did not affect the AMPAR component. Thus, postnatal Week 2 in the rat appears to be a sensitive or critical period, as least regarding exposure to exogenous nicotine.

In another test of the hypothesis, CNE has been shown to affect NMDAR development in auditory cortex. CNE altered the developmental expression of mRNA for NMDAR subunits (Hsieh et al. 2002), and prevented the normal maturation and disappearance of pure-NMDAR synapses (Hsieh and Metherate 2003). These effects of CNE may reflect disruption of the normal role of nAChRs in the development of NMDARs. Finally, in preliminary studies to determine the effect of early postnatal manipulations on sensory function, CNE during Week 2 markedly reduced the ability of systemic nicotine to enhance sensory responsiveness in adult (>2-month-old) auditory cortex (Liang and Metherate 2003; cf. "Cortical nAChRs Regulate Responses to Sensory Stimuli" above). These data indicate that early postnatal CNE can lead to nAChR dysfunction in adult animals.

The effects of CNE in the rat should be related to human development, especially in light of the possible consequences for brain development of nicotine exposure from cigarette smoking. The studies reviewed here raise the possibility that maternal smoking may alter fetal sensory cortex development, with potentially long-lasting consequences. Notably, infants born to mothers who smoke during pregnancy show auditory-related cognitive deficits as they mature, despite apparent normal hearing range and thresholds (Sexton et al. 1990; McCartney et al. 1994; Fried et al. 1997). It is possible that CNE-induced disruption of developing NMDARs and nAChR function may contribute to sensory–cognitive deficits in older children and adults.

Conclusions and Some Future Directions

A consensus is emerging on some likely functions of nAChRs in sensory neocortex. Cortical nAChRs likely act to enhance sensory responsiveness, which may contribute to improved behavioral performance in sensory–cognitive tasks. The cellular basis for this may lie in the regulation of thalamocortical glutamate release by presynaptic (or preterminal) nAChRs (Fig. 1B), and possibly in nicotinic regulation of GABAergic interneurons. Although the latter effect is clear experimentally, its consequences for sensory processing depend on how interneurons contribute to cortical circuits activated by sensory stimuli. Such a problem will be technically difficult to answer; however, it may be simplified through the use of reduced preparations, such as the thalamocortical slice.

The major roles of nAChRs identified thus far in sensory cortex appear, at first glance, similar to some roles in nonsensory cortex, which supports the idea of sensory cortex as a useful model system (given that physiological activation with sensory stimuli is possible). A clear example of correspondence between sensory and nonsensory cortex is the nAChR-mediated regulation of thalamocortical afferents in prefrontal cortex: The cellular mechanisms seem similar to those in sensory cortex, although the function of prefrontal cortex is undoubtedly quite different. Nicotinic actions in sensory cortex and hippocampus also exhibit broad similarities, for example, prominent nicotinic excitation of GABAergic interneurons. However, differences in the underlying mechanisms (e.g., nAChR subtypes) and obvious differences in circuitry preclude simple analogies at the systems level. Nonetheless, understanding the role of nAChRs in regulating sensory cortical responses to sensory stimuli should contribute to the understanding of systems-level function in other cortices.

Finally, recent studies have identified novel nAChR functions during postnatal development of sensory cortex (Fig. 1A,C). These occur at the onset of sensory function, and may define a critical period, that is, they may contribute to the shaping of synaptic circuitry by early sensory experience. Ongoing research indicates that transient exposure to exogenous nicotine during this critical period may permanently alter sensory cortex function. Such effects may underlie the sensory–cognitive deficits in children exposed prenatally to nicotine. It will be necessary to pursue both human and animal studies to test the possible link between developmental nicotine exposure and subsequent cognitive function.

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