

# Nicotinic Receptors in the Brain: Links between Molecular Biology and Behavior

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*Molecular cloning has elucidated the sequence of a family of acetylcholine receptor subunits that are activated by nicotine. Subsequent studies on the localization of individual subunits and the physiological properties of nicotinic subunit combinations in vitro, have led to identification of subunit compositions of nicotinic receptors that may function in vivo, as the native receptor. A particular challenge for the field has been to use these molecular data to determine which individual nicotinic receptor subtype is responsible for mediating each of the behavioral effects of nicotine. Human and animal studies have shown that nicotine is reinforcing and likely responsible for the addictive properties of tobacco. In*

*addition, nicotine has been shown to have effects on locomotion, cognition, affect, and pain sensitivity. Recent studies combining the techniques of molecular biology, pharmacology, electrophysiology, and behavioral analysis to analyze knock out mice that lack individual subunits of the nicotinic acetylcholine receptor, have helped identify the role of specific nicotinic subunits in some of these complex behaviors. These studies could ultimately be useful in designing specific nicotinic receptor agonists and antagonists that may have uses in the clinic.*

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The physiological effects of nicotine are mediated through binding to, and activation of, nicotinic acetylcholine receptors (nAChRs). These nAChRs are pentamers made up of subunits that have distinct, but overlapping expression patterns in subsets of neurons. Molecular cloning and *in situ* hybridization have been used to identify the expression patterns of different nAChR subunits. Parallel pharmacological studies have characterized the various behavioral actions of nicotine in the whole ani-

mal, but it has been difficult to correlate particular subunit compositions of nAChRs with these nicotine-elicited behaviors. This review will attempt to integrate what is known about the molecular, anatomical, and pharmacological properties of nAChR subunits with behavioral data, and summarize current opinions about which nAChR subtypes are responsible for particular behaviors.

## MOLECULAR BIOLOGY AND NEUROPHYSIOLOGY OF nAChRs

Upon binding of ACh or other agonists, nAChRs allow cations to flow through an intrinsic channel, generally resulting in depolarization of the neuron. To date, 11 different neuronal nAChR subunits have been identified ( $\alpha 2$ – $\alpha 9$  and  $\beta 2$ – $\beta 4$  (discussed in Le Novère and Changeux 1995). High affinity nAChRs are thought to be made up of 2  $\alpha$  and 3 non- $\alpha$  subunits per pentamer

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(Anand et al. 1991; Cooper et al. 1991), whereas a subfamily of nAChRs ( $\alpha 7$ -; $\alpha 8$ ) form functional homo-pentamers (reviewed in Role 1992; Sargent 1993).

The neuronal nAChR subunits can be divided into subfamilies based on sequence homology and phylogeny (Le Novère and Changeux 1995), as well as pharmacological and physiological properties.  $\alpha 1$ - $\alpha 6$  combined with  $\beta 2$ - $\beta 4$  would comprise one family and  $\alpha 7$ - $\alpha 8$  would comprise the second.  $\alpha 9$  has distinct pharmacological properties and is likely to be part of a third family. Functionally, nAChRs can be further divided into those containing the  $\beta 2$  subunit combined with various  $\alpha$  subunits, which have the highest affinity for nicotine (Picciotto et al. 1995), and those containing the  $\beta 4$  subunit combined with various  $\alpha$  subunits, which have 10–100 times lower affinity for nicotine (Luetje and Patrick 1991).  $\beta 4/\alpha 3$  subunit-containing nAChRs are highly expressed in the peripheral nervous system and appear to be essential for fast synaptic transmission in the autonomic ganglia (Xu et al. 1999b). In contrast, the subtypes of nAChR expressed most highly in the brain are  $\beta 2/\alpha 4$  subunit-containing receptors and  $\alpha 7$  subunit-containing,  $\alpha$ -bungarotoxin binding receptors (Flores et al. 1992; Hill et al. 1993; Wada et al. 1989; Zoli et al. 1995).

In the muscle and autonomic ganglia, nAChRs are concentrated at the neuromuscular junction or the synaptic region (Galzi et al. 1991; Rathouz and Berg 1994). In contrast, at least some subtypes of nAChR in the brain (those containing the  $\beta 2$  subunit) are located diffusely throughout the membrane of the neuron, with no obvious concentration at the synaptic junction (Hill et al. 1993). Furthermore, a large proportion of nicotine binding sites are found on nerve terminals rather than in the post-synaptic membrane (Clarke and Pert 1985).

Several effects of nicotine in the brain may be mediated through neuromodulatory potentiation of the release of neurotransmitters (including acetylcholine, dopamine (DA), glutamate, GABA, norepinephrine, and serotonin) (MacDermott et al. 1999; McGehee and Role 1996; Wonnacott et al. 1989). These effects are probably mediated through presynaptic or preterminal nAChRs, rather than through traditional neurotransmission in which pre-synaptically released acetylcholine acts on postsynaptic, junctional nAChRs to cause neuronal firing (Léna et al. 1993; Marshall et al. 1997; McGehee et al. 1995; Summers and Giacobini 1995; Vidal and Changeux 1993; Wonnacott et al. 1990; Yang et al. 1996).

Low concentrations of nicotine, consistent with the levels found in the blood of moderate smokers (Henningfield et al. 1983), are sufficient to affect neurotransmitter release and the electrophysiological properties of neurons. For example, nanomolar concentrations of nicotine have been shown to enhance excitatory transmission in cultures of neurons from the medial habenula or the hippocampus (Gray et al. 1996; McGehee et al. 1995). The increase in both ACh and glutamate release

appears to be mediated through an  $\alpha 7$  subunit-containing nAChR as it can be blocked by  $\alpha$ -bungarotoxin and is greatly diminished in the presence of antisense oligonucleotides targeted to the  $\alpha 7$  subunit. Nanomolar concentrations of nicotine can also stimulate the firing of dopaminergic neurons (Picciotto et al. 1998; Pidoplichko et al. 1997), as well as the release of DA from striatal synaptosomes (Grady et al. 1992), through an  $\alpha 4/\beta 2$ -containing nAChR. The ability of low levels of nicotine to stimulate different neuronal systems raises the possibility that endogenous ACh could stimulate non-synaptic nAChRs through a mechanism resembling volume transmission in which ACh escaping the synapse activates nAChRs some distance away (volume transmission is reviewed in Zoli et al. 1999a).

### GENETIC MANIPULATION OF nAChRs

Although there is a great deal of information about which subunit combinations are functional *in vitro*, the nAChR subunit combinations present and active *in vivo* are not yet fully identified. Pharmacological antagonists show some selectivity, but most compounds can inhibit many subtypes of nAChR *in vivo* (Decker et al. 1995). The  $\alpha$ -conotoxins appear to be fairly specific for different nAChR subunit pairs *in vitro* (Cartier et al. 1996). It is not yet known whether the functions affected by these toxins *in vivo* are carried out by the same subunits identified *in vitro*, or by subunit pairs that have not yet been tested.

One method of identifying nAChR subunits that are functional *in vivo* is to use antisense oligonucleotide to transiently decrease the expression of specific subunits. Studies using this technique are compelling, although some problems have been noted for antisense approaches, including problems of specificity, making it useful to complement these studies with other techniques that can be used to manipulate levels of nAChR subunits.

Sympathetic neurons from isolated chick sympathetic ganglia have been treated with antisense oligonucleotides to decrease the expression of  $\alpha 3$ ,  $\alpha 4$ , and  $\alpha 7$  nAChR subunits selectively (Listerud et al. 1991). In these experiments, treatment with antisense oligonucleotides targeting the  $\alpha 3$  subunit abolished one of the primary classes of nicotine-elicited currents, suggesting that this subunit has a primary role in nicotinic transmission in sympathetic ganglia. Antisense oligonucleotides targeting the  $\alpha 7$  subunit also shifted the pattern of nicotine-elicited currents, suggesting that this subunit can contribute to the observed currents. The notion that  $\alpha 3$  and  $\alpha 7$  subunits contribute to ganglionic transmission is further supported by both electrophysiological and immunoprecipitation studies (Sargent 1993).

Additional studies showed that several different cur-

rents in sympathetic ganglia involve the  $\alpha 7$  subunit. This implies that, in addition to forming homomeric nAChRs, the  $\alpha 7$  subunits may combine with other nAChR subunits to form functional receptors *in vivo* (Yu and Role 1998). Antisense studies have also shown that the  $\alpha 5$  subunit can alter the electrophysiological properties of nAChRs containing the  $\alpha 4$  and  $\beta 2$  subunits *in vivo* and is therefore likely to play an important role in nicotinic transmission in those brain areas in which it is expressed (Ramirez-Latorre et al. 1996). Studies of animals treated centrally with antisense oligonucleotides to the  $\alpha 6$  subunit have shown a role for this subunit in mediating the locomotor activating effects of nicotine, which implies that it may be involved in modulating the dopaminergic system (Le Novère et al. 1999).

Another useful tool for identifying the role of particular nAChR subunits in behavioral functions of nicotine will be the generation of knock out mice lacking specific nAChR subunits. Knock out mice have been developed lacking the  $\beta 2$  subunit (Picciotto et al. 1995), the  $\alpha 7$  subunit (Orr-Urtreger et al. 1997), the  $\alpha 9$  subunit (Vetter et al. 1997, 1999), the  $\alpha 4$  subunit (Marubio et al. 1999), the  $\alpha 3$  subunit (Xu et al. 1999a), and the  $\beta 4$  subunit (Xu et al. 1999b) (Table 1). Knock outs of the  $\alpha 5$  subunit (Xu et al. 1997) and the  $\beta 3$  subunit (Allen et al. 1998) have been also been reported.

Knock out mice have been used to demonstrate the role of individual nAChR subunits in effects of nicotine on neurophysiology. Experiments in knock out mice lacking the  $\alpha 7$  subunit have shown that a rapidly desensitizing nicotinic current in the hippocampus is mediated through an  $\alpha 7$ -containing nAChR (Orr-Urtreger et al. 1997). In addition, experiments in  $\beta 2$  subunit knock out mice have demonstrated that nAChRs on dopaminergic neurons that mediate nicotine-elicited increases in firing rate contain the  $\beta 2$  subunit (Picciotto et al. 1998). The  $\beta 2$  subunit is also involved in mediating other presynaptic responses to nicotine, including effects on GABA release (Lu et al. 1998; Marks et al. 1999).

Pharmacological and electrophysiological techniques have also been used on  $\beta 2$  subunit knock out mice to characterize nAChR subtypes in the brain (Zoli et al. 1998). Four types of nAChR subtypes have been identified (Table 2) extending the characterization of nAChRs based primarily on pharmacology (Alkondon and Albuquerque 1993). Type I nAChRs contain the  $\alpha 7$  subunit, account for all  $\alpha$ -bungarotoxin binding in the brain (Orr-Urtreger et al. 1997), and are unaltered in the  $\beta 2$  subunit knock out (Zoli et al. 1998). Type 2 nAChRs contain the  $\beta 2$  subunit and bind several nicotinic agonists with high affinity (including epibatidine, nicotine, and cytosine). This class is most potently activated by the nicotinic agonist epibatidine in electrophysiological experiments (nicotine is slightly less potent at activating these receptors and cytosine is not very potent).

Type 2 nAChRs are likely to be composed of  $\beta 2/\alpha 4$  subunits in most brain regions with other  $\alpha$  subunits contributing in specific areas. High affinity nicotine binding is completely abolished in  $\beta 2$  subunit knock out mice (Picciotto et al. 1995) and nearly absent in  $\alpha 4$  subunit knock out mice (Marubio et al. 1999). Despite the overall decrease in high affinity nicotine binding in  $\alpha 4$  subunit knock out mice, nicotine binding remains, to some extent, in the interpeduncular nucleus and epibatidine binding remains in the substantia nigra and superior colliculus. This suggests that other  $\alpha$  subunits can combine with the  $\beta 2$  subunit in these brain areas to form functional Type 2 nAChRs (Marubio et al. 1999). Binding experiments using  $\alpha$ -conotoxin MII suggest that the  $\beta 3$  subunit combines with  $\beta 2$  subunit-containing nAChRs in some brain areas, including the dopaminergic system, since  $\beta 3$  subunit knock out animals show decreased binding of  $\alpha$ -conotoxin MII, whereas knock out of the  $\beta 2$  subunit completely abolishes  $\alpha$ -conotoxin MII binding (Allen et al. 1998; Whiteaker et al. 1998).

Type 3 nAChRs are probably composed of  $\beta 4/\alpha 3$  subunits, bind epibatidine (but not nicotine or cytosine) with high affinity in equilibrium binding experiments, and respond most potently to epibatidine in electrophysiological experiments (nicotine and cytosine are equally effective agonists).

Type 4 nAChRs selectively bind cytosine and epibatidine with high affinity in equilibrium binding experiments. These nAChRs contain the  $\beta 4$  subunit and respond most potently to epibatidine, but type 4 nAChRs exhibit faster desensitization than type 3 nAChRs at high doses of nicotine. Future experiments using mice lacking other nAChR subunits should allow a finer definition of these receptor classes.

## BEHAVIORAL EFFECTS OF NICOTINE AND RELATION TO nAChR SUBTYPES

Nicotine affects many aspects of behavior including locomotion, nociception, anxiety, learning and memory, as well as behaviors associated with drug abuse (Decker et al. 1995). Several studies have also shown positive and negative associations of smoking with psychiatric and neurological illnesses. The rate of smoking is much higher in schizophrenics (up to 90%) (Nisell et al. 1995), depressed patients (up to 65%) (Breslau 1995), and alcoholics (up to 90%) (Burling and Ziff 1988) than in the general population. In contrast, smoking is negatively correlated in some studies with the incidence of Parkinson's disease and Alzheimer's disease (James and Nordberg 1995). Given the wide diversity of behavioral effects mediated by nicotine in human smokers and animal models, it seems possible that these effects are mediated through selective activation of different nAChR Subtypes (see Table 3).

**Table 1.** Knock Outs of nAChR Subunits

Subunit	Localization	KO	KO Phenotype	Refs
$\alpha 2$	Primarily IPN Some cortical layers/ olfactory nucleus	Not reported	–	Wada et al. 1989
$\alpha 3$	Autonomic ganglia Primarily MhB, dorsocaudal medulla	High mortality before and after weaning	Impaired growth, megacystis (inflamed urinary bladder) and mydriasis (widely dilated ocular pupils)	Wada et al. 1989; Xu et al. 1999a
$\alpha 4$	Some cortex, VTA Throughout brain	Viable	Reduced antinociception	Marubio et al. 1999
$\alpha 5$	Autonomic ganglia Primarily MhB, dorsocaudal medulla, hippocampus, SN	Viable	Not yet reported	Xu et al. 1997
$\alpha 6$	Some cortex Primarily LC, VTA, SN Some supramammillary, reticular thalamus, mesencephalic V	Not reported	–	Le Novère et al. 1996
$\alpha 7$	Throughout brain High in cortex, hippocampus, amygdala Low in thalamus	Viable	Largely normal Lack MLA-sensitive nicotine response in hippocampal interneurons May have slightly decreased anxiety response	Orr-Urtreger et al. 1997; Paylor et al. 1998; Seguela et al. 1993
$\alpha 9$	Cochlear hair cells, skeletal muscle of the tongue, hypophysis, nasal epithelium	Viable	Involved in cochlear efferent innervation development and function	Elgoyhen et al. 1994; Vetter et al. 1999
$\beta 2$	Autonomic ganglia throughout brain, very high in thalamus	Viable	Lack nicotine-induced increases in passive avoidance, reinforcement, antinociception Show increased neurodegeneration during aging	Marubio et al. 1999; Picciotto et al. 1995, 1998; Zoli et al. 1998, 1999b
$\beta 3$	LC, VTA, SN Wider brain expression but mostly co-localization with $\alpha 6$	Viable	Altered locomotor activity	Allen et al. 1998; Le Novère et al. 1996
$\beta 4$	Autonomic ganglia Primarily IPN, MhB, dorsocaudal medulla Some superior colliculus, medial geniculate	Viable	Viable, but lethal when combined with $\beta 2$ subunit knock out	Dineley-Miller and Patrick 1992; Wada et al. 1989; Xu et al. 1997, 1999b

Abbreviations: IPN, interpeduncular nucleus; MhB, medial habenula; LC, locus coeruleus; VTA, ventral tegmental area; SN, substantia nigra; MLA,  $\alpha 7$  antagonist methyllycaconitine.

Knock out mice have been used to examine the role of nAChR subtypes in a few of the behavioral actions of nicotine. At present, most of the information available on nAChR subtypes involved in behavior comes from pharmacological or anatomical studies. In this portion of the review, we will describe some of the behavioral actions of nicotine and attempt to correlate these data both with the anatomical locus of action of nicotine and the potential nAChR subtypes that might mediate the behavioral effect.

Only the  $\alpha 3$  subunit appears to be necessary for survival (Xu et al. 1999a). Mice lacking the  $\alpha 4$ ,  $\alpha 5$ ,  $\alpha 7$ ,  $\beta 2$ ,  $\beta 3$ , or  $\beta 4$  subunits are all viable and appear grossly nor-

mal (Allen et al. 1998; Marubio et al. 1999; Orr-Urtreger et al. 1997; Picciotto et al. 1995; Xu et al. 1997, 1999b). One drawback of studies with knock out mice that should be mentioned is that these animals lack the subunit of interest throughout development, and thus adaptations in neural circuitry may affect the interpretation of behavioral changes in these animals. Future studies of animals with conditional or inducible knock out of individual subunits will further refine the conclusions that can be drawn about the role of nAChRs in adult behavior. There are still many gaps in our knowledge of the subtypes of nAChR mediating specific behavioral actions of nicotine. However, genetic engineer-

**Table 2.** Classification of nAChR-Mediated Currents

Class	Electrophysiological Response	Ligand Binding Profile	Subunit Composition	Localization
Type 1	$\alpha$ BTX and MLA-sensitive, very fast desensitization	$\alpha$ BTX	$\alpha 7$	Throughout brain
Type 2	MLA-insensitive, NIC >>> CYT, DH $\beta$ E = MCA	EPI > NIC = CYT = MCC = ACH (high affinity for nicotine)	$\beta 2/\alpha 4$ $\beta 2/\alpha 2?$ (non $\alpha 4$ ) $\beta 2$ (non $\alpha 4$ ) $\beta 2/\alpha 6/\beta 3$ $\beta 2/?$	Throughout brain IPN SN + SC LC (type A) Hippocampus
Type 3	MLA-insensitive, CYT = NIC, DH $\beta$ E < MCA, slow decay at 100 $\mu$ m NIC	EPI (low affinity for nicotine)	$\beta 4/\alpha 3/\alpha 5?$ $\beta 4/\alpha 3$	MhB, IPN, dorsal medulla LC (type B), autonomic ganglia
Type 4	MLA-insensitive, CYT = NIC, DH $\beta$ E < MCA, fast decay at 100 $\mu$ m NIC	EPI > CYT > MCC = ACH	$\beta 4/\alpha 4?$ $\beta 4/\alpha 2?$	Lateral MhB Dorsal IPN

Based on Zoli et al. 1998 with some additional information from Léna et al. 1999; Marubio et al. 1999; and Xu et al. 1999a, 1999b.

Abbreviations: NIC, nicotine; CYT, nicotinic agonist cytisine; EPI, nicotinic agonist epibatidine; MCC, nicotinic agonist methyl carbamylcholine; ACH, acetylcholine; MCA, nicotinic antagonist mecamylamine; DH $\beta$ E, nicotinic antagonist dihydro- $\beta$ -erythroidine; MLA,  $\alpha 7$  antagonist methyllycinitine;  $\alpha$ BTX,  $\alpha 7$  antagonist  $\alpha$ -bungarotoxin; IPN, interpeduncular nucleus; SN, substantia nigra; SC, superior colliculus; MhB, medial habenula; LC, locus coeruleus.

ing has advanced the fields of behavioral pharmacology and molecular biology to allow such questions to be addressed in behaving animals.

**Nicotine Reinforcement and Withdrawal**

**Behavioral Studies.** Nicotine is thought to be the primary substance in cigarette smoke responsible for addiction to tobacco (US Department of Health and Human Services 1988) and several behavioral paradigms have been used to demonstrate the reinforcing properties of nicotine in animal models. Nicotine can condition a place preference in rodents (Shoaib et al. 1994),

although the parameters under which place preference can be conditioned are limited (Clarke and Fibiger 1987) and are likely to be affected by many environmental and genetic factors. Nicotine self-administration has also been demonstrated in several species and, again, the parameters under which animals self-administer nicotine are more limited than for cocaine self-administration. This may resemble the intermittent pattern of nicotine administration from smoking (Corrigall and Franklin 1989; Cox et al. 1984; Risner and Goldberg 1983).

Nicotine has complex effects on locomotion. In a familiar environment nicotine administration can result

**Table 3.** Potential Anatomical and Molecular Substrates for the Behavioral Actions of Nicotine

Behavior	Possible Sites of Nicotine Action	Potential nAChR Subtypes
Reinforcement	Mesolimbic DA system (VTA-NAc)	$\alpha 4/\beta 2/\alpha 6/\beta 3$
Sensitization	VTA	$\alpha 7; \alpha 4/\beta 2/\alpha 6/\beta 3$
Locomotion		
-hyper	VTA and NAc	$\alpha 4/\beta 2/\alpha 6/\beta 3$
-hypo	MHb and IPN	$\alpha 3/\beta 4; \alpha 2/\beta 4$
Antinociception	Raphe and thalamus	<u><math>\alpha 4/\beta 2</math></u>
	Spinal	non $\alpha 4$ ( $\alpha 3/\beta 4$ )
Working memory	Hippocampus, cortex	?
Fear associated learning	Amygdala, brainstem, thalamo-cortical pathway	$\alpha 4/\beta 2$
Neurodegeneration	Hippocampus	$\alpha 4?/\beta 2$
	Cortex	$\alpha 4/\beta 2$
Anxiety	Septo-hippocampal system	$\alpha 7$
Depression	Septo-hippocampal system	$\alpha 4/\beta 2, \alpha 7?$
	Hypothalamus, pituitary, adrenal axis	$\alpha 4/\beta 2, \alpha 7?$
Latent inhibition pre-pulse inhibition	NAc, PPN	$\alpha 4/\beta 2$
	Hippocampus	$\alpha 7$
	Septohippocampal system, medial raphe	$\alpha 7$

Possible nAChR subunit compositions suggested from experiments with knock out mice (underlined).

Abbreviations: VTA, ventral tegmental area; NAc, nucleus accumbens; MHb, medial habenula; IPN, interpeduncular nucleus; PPN, pedunculo-pontine tegmental area; DA, dopamine.

in locomotor activation (Clarke et al. 1988). Repeated nicotine injection also results in sensitization to further nicotine challenge (Clarke and Kumar 1983; Museo and Wise 1990), an effect that has been associated with administration of psychostimulants. In contrast, acute treatment of a naive rodent with nicotine in a novel environment results in rapid locomotor depression (Marks et al. 1989), an effect that exhibits tolerance upon subsequent nicotine injection (Marks et al. 1991).

In humans, nicotine withdrawal following smoking cessation is characterized by weight gain, irritability, anxiety, insomnia, depression, and difficulty concentrating (Hughes et al. 1994). In rats, nicotine withdrawal is similar to opioid withdrawal and involves shakes, ptosis, genital licks, teeth chatter, and changes in locomotor activity (Hildebrand et al. 1997; Malin et al. 1992). Spontaneous nicotine withdrawal in rats also results in a decrease in brain reward thresholds similar to the decrease seen with other drugs of abuse (Epping-Jordan et al. 1998). Precipitation of nicotine withdrawal by administration of a nicotinic antagonist following chronic nicotine treatment can condition a place aversion, indicating that nicotine withdrawal results in negative affect (Suzuki et al. 1996).

Several studies have also shown an interaction between nicotine and other drugs of abuse. Pre-exposure to drugs of abuse such as morphine and amphetamine can potentiate nicotine reinforcement. For example, in the brain stimulation reward model, both drugs decrease the dose of nicotine required to lower the self-stimulation threshold (Huston-Lyons et al. 1993). Conversely, prior exposure to nicotine enhances the conditioned rewarding effects of morphine (Shippenberg et al. 1996), accelerates the acquisition of ethanol drinking behavior in naive rats (Smith et al. 1999) and predisposes rats to self-administer a low dose of cocaine (Horger et al. 1992). In the place preference paradigm, nicotine can potentiate the action of low doses of cocaine, whereas antagonism of nAChRs decreases the response to a threshold dose of cocaine (Zachariou et al. 1997).

### Neuroanatomical and Lesion Studies

The reinforcing effects of nicotine are thought to be mediated via the mesolimbic DA system (the ventral tegmental area (VTA) and its projections to the nucleus accumbens (NAc)) which is known to mediate the action of many drugs of abuse (Koob 1992). Nicotine self-administration is decreased following lesion of the mesolimbic DA system (Corrigall et al. 1992). Furthermore, injection of nicotine directly into the VTA can condition a place preference (Museo and Wise 1994). The locomotor activating effects of nicotine are also mediated through stimulation of the dopaminergic system since injection of nicotine directly into the VTA or NAc re-

sults in increased locomotion (Museo and Wise 1990, 1995) and locomotor sensitization is decreased following lesion of the VTA (Corrigall et al. 1992). In contrast, nicotine-induced hypoactivity is mediated through the interpeduncular nucleus, a brain area with the highest expression of the  $\beta 4$  subunit, showing that the ability of nicotine to depress locomotion is anatomically distinct from its locomotor activating effects (Hentall and Golapudi 1995).

*In vivo* microdialysis has been used to demonstrate that nicotine can augment DA release in the striatum and NAc of rodents (Benwell and Balfour 1992; Marshall et al. 1997). The effect of nicotine on DA levels may be due in part to activation of nAChRs on DA terminals, as nicotine-elicited DA release can be seen in purified synaptosome preparations from the NAc that are highly enriched in presynaptic elements (Grady et al. 1992; Rowell 1995; Wonnacott et al. 1990). Although injection of a nicotinic agonist directly into the DA terminal fields of the NAc can stimulate DA release, the strongest effects of nicotine appear to be on the DA cell bodies of the VTA (Mifsud et al. 1989). In addition, nicotine infusion into the VTA produces a longer-lasting effect on DA release than infusion into the NAc (Nisell et al. 1994). Nicotine self-administration also results in increased expression of the chronic Fos-related antigens in the NAc (Merlo Pich et al. 1997), which are transcription factors that may be involved in neuroadaptation following chronic treatment with drugs of abuse (Kelz et al. 1999; Nye and Nestler 1996).

Changes in mesolimbic DA function are also seen following nicotine withdrawal. Nicotine withdrawal results in changes in the firing pattern of VTA neurons (Rasmussen and Czachura 1995) and mecamylamine-precipitated withdrawal results in reduced DA output in the NAc, as has been seen following withdrawal from other drugs of abuse (Hildebrand et al. 1998).

### Genetic Models

Nicotine reinforcement has been studied in knock out mice lacking the  $\beta 2$  subunit of the nAChR (Picciotto et al. 1998). In the absence of the  $\beta 2$  subunit, neurons in the DA system are grossly normal, but nicotine fails to induce DA release in the NAc, and DA neurons in the VTA become unresponsive to nicotine. Nicotine self-administration is also abolished in these mice, suggesting that the  $\beta 2$  subunit is a component of the nAChR mediating nicotine reinforcement. Studies using glutamatergic antagonists and the  $\alpha 7$ -selective antagonist methyllycaconitine in rat have suggested that  $\alpha 7$  subunit-containing receptors localized presynaptically on glutamatergic afferents in the VTA contribute to the stimulation of DA release in the NAc (Schilstrom et al. 1998a,b). Although these receptors may contribute to the stimulation of DA release in the NAc in mice (Schil-

strom et al. 1998a,b), they are less likely to be the primary mediators of nicotine reinforcement since mice lacking the  $\beta 2$  subunit showed normal levels of  $\alpha$ -bungarotoxin binding. One possibility is that the  $\alpha 7$ -mediated effect on glutamatergic terminal in the VTA is responsible for the plasticity induced by repeated nicotine treatment, and that this effect leads to sensitization of both DA release and locomotor activity following repeated nicotine treatment. Experiments using  $\alpha 7$  knock out mice will be very useful for exploring this hypothesis.

### Antinociception

**Behavioral Studies.** Both nicotine (Tripathi et al. 1982) and the nicotinic agonist epibatidine (Traynor 1998) are antinociceptive. Nicotinic compounds increase the latency for rodents to perform the tail flick response, escape from a hot plate or perform the paw lick response. Recently, a ligand which is thought to activate  $\alpha 4/\beta 2$ -containing nAChRs (ABT-594) has been developed that shows antinociceptive properties which are blocked by the nicotinic antagonist mecamylamine and which are equal in efficacy to those of morphine when tested in animal models of acute thermal, persistent chemical, and neuropathic pain (Donnelly-Roberts et al. 1998). One of the major advantages of ABT-594 is that chronic administration does not elicit opioid-like withdrawal or physical dependence (Bannon et al. 1998). These studies suggest that nAChRs containing the  $\alpha 4$  and  $\beta 2$  subunits are found on neurons in pathways modulating pain response.

**Neuroanatomical and Lesion Studies.** Nicotine-induced antinociception is mediated through both the cholinergic and opioidergic systems (Zarrindast et al. 1997) and is enhanced by agents that increase intracellular calcium through L-type channels (Damaj and Martin 1993). Nicotine can also potentiate morphine but not  $\delta$  and  $\kappa$  opioid receptor-mediated antinociception (Suh et al. 1996) and upregulates  $\mu$  opioid receptors in striatum (Wewers et al. 1999). Brain areas mediating nicotine-induced antinociception are thought to include the thalamus, raphe magnus, and the pedunculopontine tegmental nucleus (Bitner et al. 1998; Jurna et al. 1993). nAChRs are also present in capsaicin-sensitive neurons, including primary afferents and dorsal root ganglia (Roberts et al. 1995). These nociceptive pathways express many subtypes of nAChR (Zoli et al. 1995). The widespread localization of nAChRs could support a role for nicotine-induced antinociception at many levels.

**Genetic Models.** Knock out mice lacking either the  $\alpha 4$  or the  $\beta 2$  subunit have been used to identify particular nAChR subunits mediating the antinociceptive effects of nicotine (Marubio et al. 1999). The lack of either the  $\alpha 4$  or  $\beta 2$  subunit results in reduced nicotine-elicited antinociception in the hot plate test and diminished sensi-

tivity to nicotine in the tail flick test. Patch clamp recordings in areas implicated in supraspinal nicotine antinociception, such as serotonergic neurons in the raphe magnus and neurons in the thalamus, showed a loss of nicotine-elicited currents in  $\alpha 4$ -/- or  $\beta 2$ -/- mice. In contrast, recordings from superficial laminae of the dorsal horn showed a nicotine-induced augmentation of postsynaptic currents, indicating that nicotine's spinal antinociception is mediated via non  $\alpha$  receptors, most likely  $\alpha 3$  and  $\beta 4$  containing nAChRs.

### Nicotine, Learning and Memory, and Neurodegenerative Disorders

**Behavioral Studies.** Nicotine has been reported to improve performance in tests measuring several forms of learning and memory. Working memory, spatial learning, and fear-associated learning have been measured in rodents in the radial arm maze, the Morris water maze and the passive avoidance task, respectively (reviewed in Levin 1992). The effects of nicotine appear to be most robust for working memory (reviewed in Levin 1992; Levin and Simon 1998). In contrast, nicotine appears to have little effect on longer term forms of memory such as reference memory. When a degree of proactive interference is built into a working memory task, nicotine can impair learning (Dunnett and Martel 1990). Nicotine has also been reported to enhance contextual fear conditioning (Gould and Wehner 1999), as well as retention of an inhibitory avoidance response in the passive avoidance task, particularly when administered immediately post-training (Faiman et al. 1991).

Many of the observed improvements in learning mediated by nicotine, particularly those in spatial learning tasks such as the Morris maze, are not seen in unimpaired animals, but instead are only observed following aging or brain lesion (Levin 1992). Treatment of Alzheimer's patients with nicotine has been shown to attenuate the decline in some of the cognitive deficits symptomatic of the disease and is particularly effective in reversing attentional deficits (Lawrence and Sahakian 1998). One of the recognized pathologies in the brains of Alzheimer's patients is a loss of neurons in the basal forebrain complex that provide cholinergic input into neocortex. Receptor binding studies on postmortem Alzheimer's brains have also shown a reduction in high affinity nicotine binding, suggesting that  $\beta 2$  subunit-containing nAChRs are lost in these patients (Nordberg 1994).

**Neuroanatomical and Lesion Studies.** Lesions of cholinergic nuclei have been used extensively to examine modulation of learning and memory (Everitt and Robbins 1997). Nicotine has been shown to restore performance in several learning paradigms following lesions of cholinergic nuclei (Levin 1992). For example, nicotine

is able to restore passive avoidance performance in animals with nucleus basalis but not basolateral amygdala (BLA) lesions (Riekkinen et al. 1993), suggesting that nAChRs in the BLA may be a potential site for nicotinic modulation of passive avoidance. Lesioning and infusion studies show that norepinephrine release in the BLA is essential in passive avoidance learning (McGaugh et al. 1996). Nicotine may exert its effects directly by stimulating brainstem norepinephrine cells that project to the BLA (Fu et al. 1998). Alternatively, modulation of norepinephrine release in the BLA by GABA, opiate, and cholinergic agonists can alter passive avoidance learning (see McGaugh and Cahill 1997 for review). Nicotine may, thus, modulate norepinephrine release indirectly by stimulating the release of any of these other neurotransmitters. Modulatory effects of nicotine could also occur in projections from the thalamus and the cortex where sensory information is likely to be processed before converging on the BLA where memory of the event is consolidated (McGaugh and Cahill 1997).

**Genetic Models.** Two lines of nAChR subunit knock out mice have been tested in learning and memory tasks to date.  $\beta 2$  subunit knock out mice, which lack high affinity receptors throughout the brain, show a slight increase in baseline passive avoidance performance that cannot be enhanced by nicotine, implicating a  $\beta 2$  subunit-containing nAChR in mediating the effects of nicotine on this behavior (Picciotto et al. 1995). These animals also show normal spatial learning as adults, but demonstrate an impairment in spatial learning following aging, suggesting that  $\beta 2$  subunit-containing nAChRs are necessary for maintenance of cognitive function in aged animals (Zoli et al. 1999b).

Aged  $\beta 2$  knock out mice also show increased cortical and hippocampal atrophy. Thus, it is not yet known whether this spatial learning deficit is attributable to a  $\beta 2$  receptor involvement in the task, increased neurodegeneration, or both. Nicotine has been shown to protect primary cells in culture from cell death induced by excitotoxic amino acids (Borlongan et al. 1995; Marin et al. 1994) and it has been suggested that there is an inverse correlation between smoking and the incidence of Alzheimer's disease (van Duijn and Hofman 1991). These data, taken together, may suggest a neuroprotective function for nAChRs with high affinity for nicotine. Aged  $\beta 2$  knock outs also have an increased level of circulating corticosterone (Zoli et al. 1999b) which could be either a cause or a consequence of the hippocampal degeneration seen. Chronic elevation of circulating glucocorticoids can lead to selective degeneration of CA3 hippocampal neurons (McEwen and Sapolsky 1995), whereas atrophy of CA3 neurons has been shown to lead to elevated corticosterone levels (Brown et al. 1999).

$\alpha 7$  subunit knock out mice show no baseline differ-

ences in fear conditioning, spatial learning and passive avoidance compared to their wild type litter mates (Paylor et al. 1998). A subtle difference was seen in latency to find the hidden platform in the Morris Water maze test, but no differences were seen in probe trials and the authors state that the decreased escape latency may reflect a feature of these knock outs other than learning. To date the effects of nicotine or aging on these learning paradigms in  $\alpha 7$  knock out mice has not been reported and it will be interesting to see whether these mice show differential sensitivity to nicotine in learning tasks.

### Smoking, Anxiety, and Affective Disorders

**Behavioral Studies.** High rates of smoking have been seen among patients with affective disorders. This suggests that nicotine may be acting to relieve symptoms of anxiety and depression (Breslau 1995). Nicotine has been reported to produce antidepressant effects even in non-smokers (Salin-Pascual et al. 1995, 1996); however, little is known about the specific nAChR subtypes involved in the actions of nicotine in affective disorders.

Studies using behavioral models of anxiety and depression in rodents also suggest that nicotine can have both anxiolytic-like and antidepressant-like effects in animals. An anxiolytic-like effect of nicotine has been demonstrated in several tests of anxiety. These include the elevated plus maze (Brioni et al. 1993), the mirrored chamber (Cao et al. 1993), the light-dark chamber (Costall et al. 1989), fear-potentiated startle (Vale and Green 1996), and the social interaction test (File et al. 1998). Nicotine has also been shown to have antidepressant-like effects in rats in the learned helplessness (Semba et al. 1998) and forced swim (Tizabi et al. 1999) models of depression.

**Neuroanatomical and Lesion Studies.** The cholinergic septo-hippocampal system has been implicated in the control of anxiety and depression (Gray 1988). In the elevated plus maze, septal lesions (Menard and Treit 1996; Treit and Menard 1997) have been shown to have anxiolytic effects. Nicotine has also been shown to act directly on the hippocampus to produce anxiolytic effects. Administration of nicotine directly into the dorsal hippocampus produces anxiolytic-like effects in both the plus maze (Ouagazzal et al. 1999) and social interaction tests (File et al. 1998). The behavioral deficits associated with learned helplessness have been prevented by lesions to the hippocampus (Elmes et al. 1975) and the ventromedial septum (Kelsey and Baker 1983). Projections from the hippocampus to the amygdala may, therefore, be involved in forming emotional memories associated with learned helplessness-inducing shock. Nicotine may thus produce its antidepressant-like effects by acting directly on the hippocampus and/or septum, or through the projection to amygdala.

Depressed patients exhibit elevated serum concentrations of cortisol and abnormal depression of cortisol levels in response to dexamethasone treatment (Kathol et al. 1989; Rush et al. 1996). In mice, chronic exposure to corticosterone decreases  $\alpha$ -bungarotoxin binding in several brain regions including the hippocampus, and hypothalamus (Pauly and Collins 1993).

**Genetic Models.** Knock out mice lacking the  $\beta$ 2 subunit of nAChR showed no differences from wild type controls in the light-dark box, mirrored chamber, and elevated plus maze tests for anxiety-related behavior (Picciotto et al. 1997). Knock out mice lacking the  $\alpha$ 7 subunit of the nAChR were not different from wild type controls in the light-dark test; however, in an open field test  $\alpha$ 7 knock outs spent a greater proportion of total distance traveled in the center of the arena in comparison to wild type mice, suggesting  $\alpha$ 7 knock outs may show less anxiety-related behavior (Paylor et al. 1998). Furthermore, as mentioned above,  $\alpha$ 7 knock out mice located a hidden platform more quickly than wild-type mice in the Morris water maze (Paylor et al. 1998). The  $\alpha$ 7 knock out mice may show faster acquisition of the water task because they exhibit less anxiety upon exposure to water. Because basal levels of anxiety related behavior are normal in  $\beta$ 2 knock out mice, or show only subtle differences in  $\alpha$ 7 knock outs, these mice can be used to examine the effects of nicotine on tests of anxiety without baseline differences which could make interpretations of behavioral data difficult.

In the forced swim model of depression, the antidepressant effect of nicotine was observed in the Flinders Sensitive Line (FSL) of rats, but was not seen in the Flinders Resistant Line (FRL) (Tizabi et al. 1999). FSL rats, which were selectively bred for increased sensitivity to anticholinesterase agents, have been proposed as an animal model of depression (Overstreet 1993), because they have lower body weight, lower locomotor activity, increased REM learning difficulties, anhedonia when exposed to chronic mild stress, and greater immobility in the forced swim test. FSL rats have higher cytosine binding in midbrain, cortex, and striatum compared to FRL rats, although no differences in  $\alpha$ -bungarotoxin binding were observed between the two lines (Tizabi et al. 1999). These results are consistent with a possible role for  $\alpha$ 4/ $\beta$ 2-containing nAChR subtypes in pathways underlying depression and in mediating the antidepressant-like properties of nicotine.

### Smoking and Schizophrenia

**Behavioral Studies.** Epidemiological studies report high rates of smoking among schizophrenic patients, with estimates as high as 90% as compared to 20–30% in the general population (Nisell et al. 1995). One possible explanation might be that patients are smoking to help alleviate the attentional deficits associated with schizophrenia. One

model of sensory filtering or gating used to investigate the attentional deficit in schizophrenia is pre-pulse inhibition (PPI), in which the presentation of one stimulus inhibits the response to a second stimulus. Schizophrenics show abnormal sensory filtering (Adler et al. 1982; Baruch et al. 1988), and nicotine has been reported to alleviate some of these deficits (Adler et al. 1993, 1998). Animal studies also suggest that nicotine may act to facilitate sensory inhibition. Nicotine can enhance PPI in mice (Stevens and Wear 1997) and rats (Acri et al. 1991, 1994).

Another model of the attention deficit associated with schizophrenia is latent inhibition (LI), in which pre-exposure to a stimulus inhibits subsequent conditioning to that stimulus (Feldon and Weiner 1992; Gray 1998). Although one study failed to find differences in LI between smokers and nonsmokers (Thornton et al. 1996), other studies have reported that smokers have enhanced LI, which is dependent upon the pre-exposure parameters (Della Casa et al. 1999a,b). Similar findings have been reported in rats, with nicotine either enhancing or disrupting LI, depending on the pre-exposure parameters (Joseph et al. 1993; Rochford et al. 1996).

**Neuroanatomical and Lesion Studies.** Electrolytic lesions of the NAc disrupt PPI (for review see Swerdlow et al. 1992). Nicotine increases DA release in the NAc, suggesting that it may mediate PPI through its effects on DA systems. However, it is unlikely that nicotine acts directly to enhance PPI through this system, because increased DA levels have been shown to disrupt PPI (Weiner and Feldon 1997). Lesions of the pedunculo-pontine nucleus have also been shown to block PPI (Swerdlow et al. 1992), and nicotine may act directly on this nucleus to enhance PPI. Lesions of the hippocampus, septum, medial raphe (for review see Weiner 1990), and NAc (for review see Weiner and Feldon 1997) disrupt LI. Since agents that promote DA release, such as amphetamine, block LI, it is thought that nicotine may act to disrupt LI by promoting DA release in NAc (Weiner and Feldon 1997). Nicotine may also act to enhance LI through direct effects on nAChRs in the septo-hippocampal system.

One brain area that may mediate the effect of nicotine on sensory gating in schizophrenia is the hippocampus. Postmortem studies have shown a reduced number of  $\alpha$ -bungarotoxin-sensitive nAChRs in the hippocampus in schizophrenic patients (Freedman et al. 1995). In rats, infusions of the cholinergic agonist carbachol into the hippocampus disrupt PPI (Caine et al. 1991). In mice, PPI has been correlated with the number of  $\alpha$ -bungarotoxin binding sites in the hippocampus. Inbred mouse strains (such as the DBA/2J strain) that showed the poorest PPI, also had the smallest numbers of  $\alpha$ -bungarotoxin binding sites (Stevens et al. 1996). Pharmacological studies also provide evidence for a role of the  $\alpha$ 7 nAChR in PPI in rodents. The nicotinic

agonists GST21, DMXBm, and DMAC, which act on the  $\alpha 7$  receptor, normalized PPI in DBA mice (Stevens et al. 1998). In rats, PPI was attenuated by central administration of  $\alpha$ -bungarotoxin (Luntz-Leybman et al. 1992) and central injections of antisense oligonucleotides to the  $\alpha 7$  subunit (Rollins et al. 1993). However, the non- $\alpha 7$ -selective nicotinic agonists cytisine and lobeline can augment LI under the same conditions that nicotine increases LI, suggesting that activation of nAChRs that do not contain the  $\alpha 7$  receptor can augment attention in the LI model (Rochford et al. 1996).

**Genetic Models.** The PPI deficit in schizophrenic patients has been linked to chromosome 15q13–14, in the region of the  $\alpha 7$  subunit gene (Freedman et al. 1997). Adult  $\alpha 7$  knock out mice show normal PPI, however (Paylor et al. 1998). These data suggest that the  $\alpha 7$  subunit of the nAChR is not responsible for baseline differences in PPI in mice, but it is possible that the  $\alpha 7$  subunit may mediate the enhancement of PPI by nicotine. Future studies with  $\alpha 7$  knock out mice can be used to address this issue.

## CONCLUSIONS

The combination of behavioral, pharmacological, anatomical, and genetic techniques has begun to resolve the question of which subtypes of the nAChR mediate the various effects of nicotine and where in the brain these actions occur. Mice have now been generated that lack most of the individual subunits of the nAChR and have been used to begin to elucidate the subtypes responsible for nicotine's effects on reinforcement and learning. Future experiments with animals lacking combinations of subunits, or lacking nAChRs only in particular brain regions or at particular times during development will be very useful in continuing this work. Ultimately, these data should be useful in developing specific nicotinic agonists that may be used to treat cognitive or affective disorders.

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