Schizophrenia, Sensory Gating, and Nicotinic Receptors

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Abstract

A series of human and animal investigations has suggested that altered expression and function of the α7-nicotinic cholinergic receptor may be responsible for the auditory sensory gating deficit characterized in schizophrenia patients and their relatives as diminished suppression of an auditory-evoked response (P50) to repeated stimuli. This finding, in conjunction with evidence for familial transmission of this sensory gating deficit, suggests a pathogenic role of the gene for the α7-nicotinic receptor in schizophrenia. This article considers the possible effects of this dysfunction in a broader context. Not only is this dysfunction consistent with difficulties in sensory gating, but it might also predispose patients to problems with learning efficiency and accuracy. Such learning problems could underlie schizophrenia patients' delusional thinking, hallucinations, and social dysfunction. In addition, heavy smoking in many schizophrenia patients is consistent with the high concentration of nicotine necessary to activate the receptor and with the receptor's extremely rapid desensitization. Finally, the receptor's possible role in cell growth and differentiation should be considered in connection with developmental deficits and other cellular abnormalities in schizophrenia.

Key words: Acetylcholine, hippocampus, habituation, interneurons.

***Schizophrenia Bulletin,* 24(2):189–202, 1998.**

One of the goals of electrophysiological and other neurobiological investigations of schizophrenia has been to elucidate deficits in elementary neuronal mechanisms that may underlie more complex symptoms such as hallucinations and delusions. A recent review in the *Schizophrenia Bulletin* outlined results from our investigations in patients, their families, and animal models, which traced the deficit in schizophrenia patients' auditory sensory gating to the α7-nicotinic cholinergic receptor (Leonard et al. 1996). Finding the specific gene mutation responsible for the inheritance of schizophrenia is an important scientific aim, but it is also necessary to consider to what extent various pathophysiological features of the illness can be explained by a specific gene defect that alters a particular neuronal mechanism, which is the theme of this issue of the *Bulletin.* This article summarizes findings implicating the α7-nicotinic receptor in schizophrenia and then shows how its dysfunction could affect patients' sensory perception and learning mechanisms in various brain areas. The article also suggests how heavy tobacco use among schizophrenia patients is related to the α7-nicotinic receptor and outlines the possibility that cholinergic neurotransmission is a potential therapeutic target for new antipsychotic medication. Finally, the article discusses implications for the pathogenesis of schizophrenia that arise from studies of effects of the α7-nicotinic receptor on cell growth and differentiation.

This review integrates the results of previously published physiological studies in humans and animal models into a hypothesis of the neuronal basis of psychological dysfunction in schizophrenia. Some philosophers believe that such interpretative attempts are inherently flawed, because the phenomena described in the framework of one realm, such as psychology, cannot be rigorously described in terms of another, such as neurophysiology (Churchland 1986). However, the historical contribution of medicine has been to connect specific biological abnormalities with human dysfunctions by examining the two simultaneously in disease states. In this historical context, we feel that it is reasonable to attempt to connect a specific neurophysiological abnormality in schizophrenia with psychological and symptomatic dysfunction.

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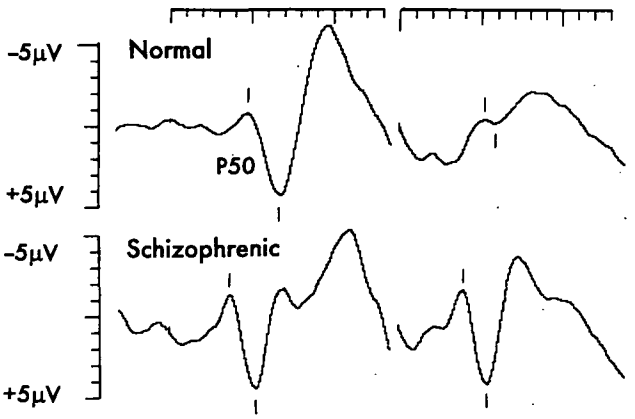
The α7-Nicotinic Cholinergic Receptor and Schizophrenia

Sensory Gating Abnormalities and Schizophrenia. Schizophrenia patients have diminished capacity to filter out unimportant features of their environment; their attention is drawn capriciously to many details that other persons would ignore (Venables 1964). Their preoccupation with these details can lead to misperception of their environment and perhaps to the hallucinations and delusions characteristic of their illness. For example, schizophrenia patients are often unable to filter out the sound of a ventilation motor, a sound that others can hear but generally ignore. The cycling of the motor can sometimes become part of the patient's delusional beliefs, taking on significance as a sign from an external force. To investigate the neurobiology of such phenomena, we have used the P50 wave, a midlatency auditory-evoked potential, to characterize differences in filtering of auditory information between schizophrenia patients and normal subjects (Adler et al. 1982). The auditory stimuli are delivered in pairs, so that the first stimulus activates inhibitory gating mechanisms that are responsible for diminishing the response to the second stimulus (figure 1). The ratio of amplitudes of the second P50 wave to the first is a measure of the activity of the inhibitory gating mechanism. Normal subjects have significantly lower ratios (mean 17.8% ± standard error of the mean [SEM] 17.0%; n = 43) than schizophrenia subjects (100.1% ± 31.8%; n = 37; t = 14.6, degrees of freedom [df] = 78, $p < 0.001$) (Waldo et al. 1994). These data and similar data from other laboratories (Boutros et al. 1991; Erwin et al. 1991; Judd et al. 1992; Vinogradov et al. 1996; see also Kathmann and Engel 1990) suggest that schizophrenia patients have a defect in an inhibitory gating mechanism. This defect is not normalized by treatment with the typical antidopaminergic neuroleptic drugs used in schizophrenia, such as haloperidol, and therefore is likely related to a neuronal mechanism independent of dopaminergic neurotransmission (Freedman et al. 1983; Adler et al. 1990). About half of the first-degree relatives of schizophrenia patients share this defect in the inhibitory gating of the P50 wave (Siegel et al. 1984). Thus, the defect may be the neurophysiological expression of part of the genetic risk for schizophrenia.

Animal Models of Sensory Gating Deficits and Related Postmortem Studies. The rat P20–N40 wave, recorded from the cornu ammonis (CA)3 and 4 regions of the hippocampus, shows suppression of response to repeated stimuli similar to that of the human P50 wave. This animal model was used to identify possible mechanisms of

Figure 1. Examples of averaged evoked potentials in response to repeated sounds from a normal and a schizophrenia patient



Sounds were delivered at the beginning of each tracing (arrows). A computer algorithm identified the P50 (marks below each tracing) and measured it relative to the preceding negative trough (marks above each tracing).

the deficit observed in schizophrenia (Bickford-Wimer et al. 1990). In animals, suppression of response is lost after lesion of the fimbria-fornix, the pathway from the septal nuclei to the hippocampus that contains, among other tracts, the cholinergic afferents to the hippocampus (Vinogradova 1975; Harrison et al. 1988). To determine if a cholinergic mechanism is involved in the inhibitory gating of the P20–N40 response to repeated stimuli, we administered various cholinergic antagonists intraventricularly while recording the hippocampal evoked response. Scopolamine and mecamylamine, which block muscarinic and high affinity nicotinic receptors, respectively, did not alter the inhibitory gating of response. However, α-bungarotoxin, which blocks a lower affinity population of nicotinic receptors, blocked the inhibitory gating of P20–N40, producing a physiological defect similar to that observed with the P50 wave in schizophrenia patients (Luntz-Leybman et al. 1992). Radio-labeled α-bungarotoxin binds diffusely throughout the hippocampus; but there is particularly intense labeling of a small population of neurons in CA3 and the dentate hilus, a subpopulation of the neurons of this region containing gamma-aminobutyric acid (GABA) (Freedman et al. 1993). Cholinergic afferents, by activating these α-bungarotoxin-sensitive receptors, may excite inhibitory neurons, which then discharge in prolonged fashion to produce a long-lasting inhibition of the response of pyramidal neurons to afferents from the perforant path (Miller and Freedman 1995).

Evidence that a defect in nicotinic cholinergic mechanisms might indeed be present in schizophrenia comes

from studies of postmortem brain tissue from schizophrenia patients. In such tissue, the cholinergic innervation of the hippocampus appears to be intact (Karson et al. 1993), so the defect may be at the receptor level. We have found diminished α-bungarotoxin labeling of apparent interneurons, as well as decreased binding of cytisine in postmortem samples of hippocampus from schizophrenia patients, compared with tissue samples from normal subjects matched for age, sex, and smoking history (Freedman et al. 1995). These findings suggest the presence of cholinergic receptor deficits, although there are other possibilities, such as absence of the GABAergic neurons that normally carry such receptors.

Other investigators have found that GABAergic neurons are hypofunctional in other brain areas of schizophrenia patients (Benes et al. 1992). In some areas, the neurons appear to be absent (Benes et al. 1991). In other areas they appear to be present, but they do not express messenger ribonucleic acid (mRNA) for the GABA synthetic enzyme glutamic acid decarboxylase (Akbarian et al. 1995). This decreased expression has been hypothesized as secondary to decreased synaptic activation of these inhibitory neurons. Failure of cholinergic excitation of the neurons is a possible mechanism response for their decreased activation and function.

The α-bungarotoxin-sensitive nicotinic receptors have been most closely associated with the α7-nicotinic receptor subunit (Schoepfer et al. 1990). Experiments in isolated cells, such as frog oocytes, show that five α7 subunits form the α-bungarotoxin-sensitive receptor. In human and rodent hippocampus, α7 subunit mRNA is expressed (Freedman et al. 1995). Mouse strains with diminished expression of the α7 gene also have diminished α-bungarotoxin binding and diminished N40 auditory response gating (Stevens et al. 1996). Thus, the gene for the α7-nicotinic receptor subunit is a candidate for the genetic transmission of sensory gating deficits in schizophrenia.

Genetic Studies of Sensory Gating Deficits in Schizophrenia. Because the deficit in inhibitory gating is distributed in families of schizophrenia subjects in a pattern consistent with autosomal dominant transmission, it is possible to determine if there is linkage to a specific chromosomal location. We have recorded P50 evoked potentials in nine moderate-sized, multigenerational families: 36 schizophrenia patients and 88 unaffected relatives. The overall linkage results were not significant, with no lod scores (log to the base ten of the odds ratio) over 3.0 for either P50 ratio or schizophrenia as a phenotype (Coon et al. 1993). Because schizophrenia may be a genetically heterogeneous illness, each family was analyzed individually for evidence of linkage, and simulations were made to determine the 95 percent confidence limits of lod scores for unlinked markers. Scores over this limit for any family would indicate an area of possible interest. For the nine families, four locations with lod scores for the P50 ratio phenotype exceeding the 95 percent confidence limit were found and verified by a flanking marker that also had a positive lod score for schizophrenia. For one family, this pattern of positive scores was on chromosome 4, for another it was on chromosome 7, for a third it was on chromosome 11; for two families, the location was on chromosome 15 at band q14. Although the lod scores at these locations exceed the 95 percent confidence limits for unlinked markers, they are still well below 3.0, the accepted threshold for linkage.

Nonetheless, the 15q14 location is of interest because it was subsequently found to be the site of the gene for the α7-nicotinic receptor subunit (Chini et al. 1994). A followup study using D1551360, a polymorphic marker isolated from a yeast artifical chromosome containing the α7 subunit gene, showed a significant linkage at this site (lod score = 5.4 at 0 recombination, $p < 0.001$ (Freedman et al. 1997). Thus, two independent lines of evidence point to the possibility that the α7 receptor contributes to the pathophysiology of schizophrenia: (1) the animal modeling of a physiological deficit found in schizophrenia subjects and (2) linkage analysis of the deficit in the families of schizophrenia subjects. Further investigation is required, however, to determine whether there are mutations in the α7 gene in schizophrenia patients that are responsible for the linkage signal and that produce a functional abnormality in the receptor, resulting in the pathological sensory processing observed in the illness. Nevertheless, sufficient information points to the α7-nicotinic receptor to prompt further consideration of how its dysfunction might be manifest in various aspects of schizophrenia.

α7-Nicotinic Receptor and the Neurobiology of Psychosis

Sensory Gating and Learning. The original observation of a P50 gating deficit at the 500 ms interstimulus interval was made empirically, by considering intervals between the first and second stimulus from 75 to 8,000 ms. Most schizophrenia patients do not have a deficit in suppression when the two stimuli occur 75 to 100 ms apart and their deficit is maximal at 500 ms (Nagamoto et al. 1991). The normal suppression of P50 and other middle- to long-latency evoked potential waves was initially thought to be caused by the neurons' need to recover their excitability after their discharge in response to the first stimulus (Davis et al. 1966). However, most of the refractory period was subsequently shown to be a result of active inhibitory mechanisms rather than neuronal fatigue

(Eccles 1969). Recovery of excitability is now understood to occur within 2 to 3 ms (Koester et al. 1991). The functional importance of the differences between schizophrenia patients and normal subjects at the interstimulus interval of 500 ms may relate to studies of animal and human learning. In animals, conditioning of skeletal muscle reflexes is maximal when the conditioned and unconditioned stimuli are separated by 500 ms (Frey and Ross 1968). Verbal learning in humans is also optimum when stimuli are approximately 500 ms apart (Conrad 1957). Sensory inhibition may be maximal when learning is optimal so that formation of associations to extraneous sensory features is minimized. Thus, a function of inhibitory gating of sensory input may be to limit the input to learning centers of the brain so that only the most important information is learned.

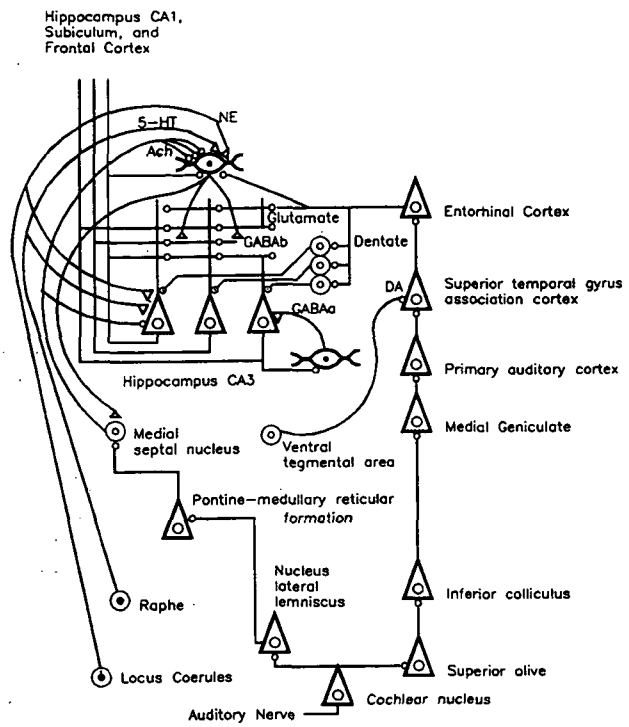
Broadbent (1971) was the first to suggest that learning and memory mechanisms have a limited capacity that must be protected from excessive stimulation for optimal learning to occur. His hypothesis has engendered much discussion and revision (Cowan 1995) based on theoretical and experimental work, but his framework remains central to most models of learning and memory. Most revisionists suggest that there is more than one filter, so that material is excluded at a number of processing levels. Furthermore, the filter is only relative, and therefore very important material, such as a person's name, can almost always be perceived. Finally, the filter appears to be simple, in essence a habituation to identical stimuli; thus, the filter excludes most repetitive information to ensure that only the most important associations between stimuli are learned. Some of these parameters of the filter are similar to those of the P50 auditory gating mechanism. P50 gating is a simple habituation easily breached by directing the subject to respond to changes in pitch in the second or test stimulus (Guterman et al. 1992). In addition, its neurobiological location places it directly in the path of information flow to the primary learning system of the brain, exactly where Broadbent's hypothesis suggested.

Evidence that such a filtering mechanism may indeed affect sensory processing comes from a comparison of the performance of schizophrenia patients and normal subjects in an auditory signal detection task (Hammond and Gruzelier 1978). The two groups had nearly equivalent performance when the stimuli occurred at 1 sec intervals. However, when the interstimulus interval was decreased to 500 ms, the normal subjects increased their detection of signals, while the schizophrenia patients decreased their performance. The percentage of failures among schizophrenia patients became twice that of the normal subjects when the stimuli were presented 500 ms apart. Like the abnormality in P50 gating, the schizophrenia patients' decreased ability to detect auditory signals at 500 ms intervals was not improved by chlorpromazine treatment. Examination of the neuronal circuitry of sensory gating, as understood from physiological investigations at the single neuron level in animals, may provide a model for understanding how sensory gating dysfunction leads to decreased psychological performance in schizophrenia.

Sensory Gating and the Hippocampus. The hippocampus is divided into the dentate gyrus, which contains the granule cells, and areas CA1–CA4, which contain the pyramidal cells. It also has contiguous neocortical areas that are closely related to its functioning: the subicular complex and the entorhinal cortex. The entorhinal cortex receives polymodal sensory input from association areas throughout the neocortex. Directly through the perforant pathway and indirectly through the dentate gyrus mossy fiber projections, the entorhinal cortex conveys this sensory information to the pyramidal cells of the CA3 region. The CA3 region receives a second type of input as well: brain stem neurons project directly to CA3 from the noradrenergic locus coeruleus and the serotonergic raphe nucleus. The brain stem reticular formation also influences the hippocampus indirectly, via the cholinergic forebrain nuclei (Bickford et al. 1993). Thus, CA3 is a major point of convergence for cortical and brain stem inputs (figure 2).

The CA3 pyramidal neurons are highly interconnected by their excitatory synapses, so that any single neuron is capable of influencing the discharge of others for at least 1.2 mm, a distance encompassing more than 10,000 pyramidal cells (Rolls 1990). In the primate hippocampus, it is estimated that each pyramidal neuron is contacted by more than 2 percent of the other pyramidal neurons, a remarkable degree of convergence. This neural network has been proposed to subserve short-term memory functions. About 10 percent of the neurons of CA3 are inhibitory. Although all of the inhibitory neurons use GABA as their inhibitory neuronal transmitter, their functions vary. Some of the inhibitory neurons activate $GABA_A$ receptors on pyramidal cells and function as a feedback inhibition circuit. These receptors provide a short, less than 50 ms, inhibition that prevents this highly interconnected excitatory network from developing uncontrolled excitatory activity, which would lead to a seizure (Eccles 1969). Other inhibitory neurons activate $GABA_B$ receptors. Some of these $GABA_B$ receptors are on the pyramidal cell bodies and provide a slightly longer inhibition, lasting up to 300 ms that supports the role of the $GABA_A$ feedback pathways. However, $GABA_B$ receptors are also found on presynaptic terminals of several types of excitatory inputs to the pyramidal cells, including the input from the granule cells and from other CA3 pyramidal cells (Isaacson et al. 1993).

Figure 2. Diagram of the inputs to the CA3 pyramidal neuron network



Inputs are shown for three interconnected neurons in the center of the diagram. The column of neurons on the right is the classical lateral lemniscal pathway, which brings auditory information from the auditory nerve to the neocortex. Through various association areas, the sound reaches the entorhinal cortex input to the hippocampus, as described in the text. Dopaminergic input facilitates transmission over this pathway, which may contribute to symptoms of acute psychoses and explain their amelioration by antidopaminergic drugs. Auditory input also reaches the reticular formation via the nucleus of the lateral lemniscus. This input activates cholinergic forebrain pathways, which in turn excite hippocampal inhibitory neurons, shown at the top. The inhibitory neurons also receive adrenergic and serotonergic inputs. These inhibitory neurons inhibit the response of the pyramidal neuron network to sensory stimulation by presynaptic gamma-aminobutyric acid $(GABA)_B$ receptors on afferent-excitatory afferent synapses to the pyramidal neurons. Many of these excitatory synapses are recurrent collaterals from other pyramidal neurons. Thus, the cholinergic stimulation of the interneurons regulates the response of the entire CA3 network to sensory input. NE = norepinephrine; 5-HT = 5-hydroxytryptamine; Ach = acetylcholine.

$GABA_B$ mediated presynaptic control of excitatory transmitter release may be a critical mechanism in the gating of sensory response (Duter and Nicoll 1988). In the paired stimulus paradigm, the first auditory stimulus activates the pyramidal cells through the perforant path input from the entorhinal cortex and the granule cell input from the dentate gyrus. The cholinergic input from the basal forebrain is also activated so that there is a 50 ms burst of activity in the pyramidal cells as their entire network excites itself (Miller and Freedman 1995). The excitatory postsynaptic potentials associated with this massive excitation give rise to the P50 wave observed on the scalp surface. The inhibitory neurons, especially those that likely activate $GABA_B$ receptors, are also activated by the first stimulus. These neurons receive a particularly intense activation because of their concentration of α7-nicotinic receptors. These nicotinic receptors form channels that admit large amounts of calcium into the cells, which sustains a long-lasting excitation (Vijayaraghavan et al. 1992). *N*-methyl-D-aspartate receptors, which have a similar ability to admit calcium, have also been shown to cause a long-lasting excitation of inhibitory neurons in the hippocampus (Grunze et al. 1996). While the resultant increased activity of the interneurons continues, the second auditory stimulus arrives. Although the perforant path input is not inhibited by presynaptic $GABA_B$ receptors, release of glutamate from the granule cell mossy fiber synapses and from the recurrent pyramidal cell synapses is inhibited (Hershman et al. 1995). Thus, the second stimulus can engender only a modest excitation of the pyramidal cells and not the burst of recurrent excitation elicited by the first stimulus. The P50 response to the second stimulus is thereby diminished. The subject hears both stimuli, but the first excites a large portion of CA3 pyramidal neurons, while the second excites a much more restricted population of neurons.

Two computer-based models of the cholinergic innervation of the CA3 pyramidal neuron network have been constructed; both reveal interesting properties of this system. The first was constructed specifically to model the circuits responsible for gating auditory response (Flach et al. 1996*a*). It used realistic parameters for hippocampal pyramidal and inhibitory neurons and postulated that postsynaptic nicotinic receptors were present on both pyramidal and inhibitory neurons, in accordance with the observed location of α-bungarotoxin binding at the electron microscopic level by Hunt and Schmidt (1978). Gating of response was lost when the input to these nicotinic receptors was removed, consistent with the loss of gating after fimbria-fornix lesion or α-bungarotoxin administration. The effect of varying the ratio of receptor number on the two types of neurons was modeled: maximal gating occurred when the inhibitory neurons had three times the number of receptors found on the pyramidal neurons. This finding is consistent with the histological finding of greater concentration of nicotinic receptors on the cell bodies of GABA-containing neurons than on pyramidal neurons (Freedman et al. 1993).

A second model, constructed by an independent group, also suggests a gating role for cholinergic innervation of the CA3 network (Hasselmo et al. 1995). This model postulates that cholinergic input affects the release

of excitatory neurotransmitter from afferents to the CA3 pyramidal neurons. Such effects have been shown to occur directly (McGehee et al. 1995) as well as indirectly through the stimulation of GABA-containing neurons that then activate $GABA_B$ receptors on excitatory presynaptic terminals (Isaacson et al. 1993). This model accounts for autoassociative memory functions of the hippocampus such as the ability to recognize that a new stimulus resembles one that was recently presented. It postulates that excitatory synapses between pyramidal neurons increase their strength whenever they are activated. This facilitation of synaptic transmission depending on use, first suggested by Hebb (1949), enables the CA3 region of the hippocampus to capture sensory input and reproduce or recall it when stimulated again by a subset of the input's features. Thus, the hippocampus can store the spatial features of a room and recall them when a portion of the room, such as a door, is presented. At the neuronal level, the first stimulus alters the activity of pyramidal neurons and thereby changes the strength of excitatory connections between the neurons, while the second stimulus reactivates the excitatory pattern that is now determined by the relative strength of synapses between the neurons.

Hasselmo et al. (1995) point out that the utility of the network depends on precise regulation or gating of the intensity of the synaptic input, which they suggest is mediated by cholinergic receptors. Referring to neurophysiological experiments in the in vitro hippocampal slice, they suggest that cholinergic input inhibits afferent input to CA3 and thus performs a gating function. During high cholinergic activity, old memory is recalled; during low activity, new memory is formed. Hasselmo et al. have not yet determined the receptor basis of this cholinergic effect. However, we can extrapolate that the absence of cholinergic activity, caused by a cholinergic receptor deficit in schizophrenia, would result in perceptual difficulties because the affected individual would constantly be altering the autoassociative memory by overstimulating it, instead of recalling previous memories to place new sensory input in the context of previous experience.

In other models of autoassociative networks (Kohonen 1984), the proper activation of recurrent inhibitory neurons is also critical to prevent cross-talk between the pyramidal neurons. The high degree of excitatory interconnections would cause activation of one pyramidal neuron to result in the activation of many pyramidal neurons. The result might be consistent with the loosening of associative memory characteristic of schizophrenia patients' formal thought disorder. Activation of dopaminergic inputs, which may increase the flow of information into the hippocampus by facilitating sensory activation of neurons in related neocortical areas (Johnson et al. 1983), also appears to increase the cross-talk between neurons (Flach et al. 1996*b*).

Information processed in CA3 is output to the CA1 pyramidal neurons. The CA1 pyramidal neurons are the principal site of long-term potentiation, a form of more extended short-term learning. Selective CA1 deficits in humans cause nearly complete loss of new learning (Zola-Morgan et al. 1986). The CA3 network helps CA1 make associations with important effects on behavior and protects it from flooding by irrelevant, repetitive stimuli. If the sensory gating mechanism fails, then we might expect two functional consequences. First, learning efficiency would be diminished because patients would have difficulty differentiating what is important to learn from extraneous information. Second, incorrect learning might occur. To return to the example of the ventilator motor whose noise the schizophrenia patient finds impossible to ignore, because of the low cholinergic activity in schizophrenia patients, the sound might reset CA3 patterns of activity and become part of the memory then encoded by CA1. Thus, a patient would fail to learn meaningful information and would associate to the sound instead. The resolution might be the paranoid delusion that the ventilator motor was causing the patient's failure in social function. Indeed a recent study of neuropsychological dysfunction in schizophrenia suggests that attentional and learning difficulties account for most social problems of schizophrenia patients (Green 1996).

Learning in a model hippocampal network consisting of modifiable synapses depends on two factors. One is that the network receives the correct amount of information during both the learning and the recall phases. The other is the capacity of the network: the number of neuronal elements present in relation to the complexity of input and output to be mastered. In such networks, loss of neuronal elements causes loss of learning efficiency and accuracy as well. Clinical studies reviewed below suggest that the presence of both a sensory gating deficit and diminished hippocampal volume may be necessary to produce the full clinical syndrome of schizophrenia, with its attendant learning difficulties and psychotic thought disorder. Thus, the sensory gating deficit may predispose an individual to learning dysfunction, but additional hippocampal pathology may be critical for that learning dysfunction to become manifest and for psychosis to develop.

Learning and Attentional Difficulties in Schizophrenia Patients and Their Relatives. Several studies support a distinction between attentional or sensory gating deficits and learning deficits in schizophrenia. This distinction emerges from comparisons between the neuropsychological performance and brain structure of schizophrenia subjects and those of their family members. If schizophrenia

is a multifactorial illness, with both genetic and nongenetic causes, then family members might show some of the deficits in isolation from the full array found in schizophrenia patients. In one study of schizophrenia patients and their parents, we selected families in which one of the parents of an offspring with schizophrenia had an additional family history of schizophrenia, making that parent likely to be an obligate carrier of schizophrenia-related genes. The other parent had no such history. Both the obligate carrier and the offspring with schizophrenia had similar problems with a group of attentional measures on neuropsychological testing. However, neither parent shared the problems in short-term verbal learning found in their offspring with schizophrenia (Harris et al. 1996).

A similar comparison of schizophrenia patients with their siblings who also had the P50 auditory gating deficit showed that the siblings had a higher full-scale performance and verbal intelligence quotient than the schizophrenia patients. Although the P50 gating deficits were similar, the nonaffected siblings had larger hippocampal volume on magnetic resonance imaging than the schizophrenia probands. The hippocampal volumes were positively correlated with intelligence quotients (Waldo et al. 1994). Study of monozygotic twins discordant for schizophrenia has shown a similar difference in learning efficiency and hippocampal volume between the twins (Suddath et al. 1990). Thus, there is converging evidence that a genetic influence, expressed as a sensory gating defect and as attentional difficulties, when combined with a smaller hippocampus and the resultant diminished learning efficiency, gives rise to clinically significant psychotic behavior.

Although these theoretical and clinical arguments have been made in terms of a single neuronal area, the CA3 region of the hippocampus, α7-nicotinic receptors are expressed throughout the brain, often in association with inhibitory interneurons. In humans, a particularly prominent expression of α7-nicotinic receptors is on the neurons of the reticular nucleus of the thalamus, which controls the flow of information to much of the neocortex (Leonard et al. 1996). Thus, the pathophysiological mechanisms modeled in the hippocampus may actually involve neuronal activity in many brain areas.

The α7-Nicotinic Receptor, Smoking, and Antipsychotic Treatment

Heavy Tobacco Smoking in Schizophrenia Patients. The possible involvement of the α7-nicotinic receptor in the sensory processing abnormalities of schizophrenia patients prompted a reexamination of the biological significance of their smoking behavior. The prevalence of tobacco smoking in schizophrenia patients is between 74 and 92 percent compared with 35 to 54 percent for all psychiatric patients and 30 to 35 percent for the general population (Hughes et al. 1986). Because nicotine reduces neuroleptic-induced extrapyramidal side effects, some investigators have hypothesized that increased smoking is associated with neuroleptic treatment (Miller 1977). However, an epidemiological study in a State mental hospital population found smoking to be related to a diagnosis of schizophrenia independent of neuroleptic treatment (de Leon et al. 1995). Smokers who have schizophrenia are also more likely to use high nicotine cigarettes and to extract more nicotine from cigarettes, even when smoking the same number as other smokers (Olincy et al. 1997).

Heavier smoking by schizophrenia patients could simply be the result of metabolic or central nervous system tolerance induced by their long exposure to nicotine, or their increased intake could reflect an attempt to use nicotine for a specific pharmacodynamic effect. Nicotine acts at multiple receptor sites in the brain. Several central nervous system nicotinic receptor subunits (α2, -3, -4, -5 and β2, -3, -4) form high affinity receptors that can be activated by a low dose of nicotine with mean effective concentration (EC_{50}) of 1 μmol (Marks and Collins 1982). Other subunits, particularly α7, form receptors that are much less sensitive to nicotine, with EC_{50} of 20 μmol (Séguéla et al. 1993). Most smokers who do not have schizophrenia probably use nicotine to stimulate high-affinity receptors, which facilitate release of GABA and dopamine, among other actions (Kirch et al. 1987; Grady et al. 1994). Thus, activation of high-affinity receptors, which could be accomplished by smoking a single cigarette, may be responsible for the decrease in anxiety and elevation of mood noted by most smokers. The higher doses of nicotine that schizophrenia patients receive by smoking several cigarettes in succession and extracting more nicotine from them might reflect their targeting of the lower-affinity α7 receptor, in addition to the high-affinity receptors.

Nicotine Corrects Sensory Gating Deficits in Schizophrenia Patients and Their Relatives. To assess possible differences in the neurobiological effect of smoking in normal smokers and schizophrenia patients, we examined the effect of their self-determined levels of cigarette smoking on the gating of the P50 auditory evoked response. Ten schizophrenia patients were studied before their first morning cigarette and found to have deficient P50 gating. They were then allowed to smoke as many cigarettes as they wished; most smoked three. After smoking, the patients had evoked potentials showing normal P50 gating, but the effect was transient and had largely disappeared by 30 minutes after smoking. Ten normal

smokers tested in the same protocol smoked about 50 percent less, but the variance of smoking behavior in both patients and normals prevented the differences in smoking intensity from reaching significance. The effect of smoking was quite different in the normals: they showed a modest decrease in normal baseline P50 gating, perhaps consistent with the release of catecholamines from activation of the low-affinity nicotinic receptors found on presynaptic terminals (Adler et al. 1993).

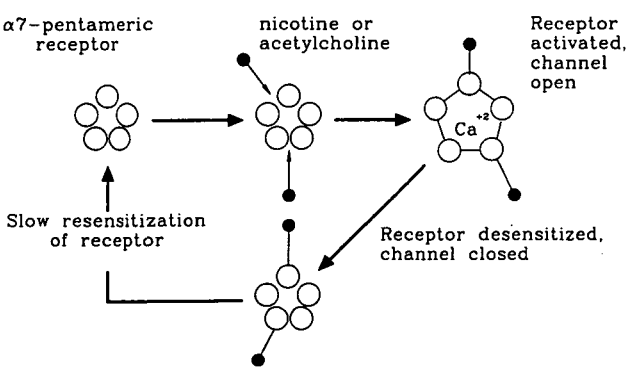
A response similar to the response in schizophrenia patients was also observed after chewing gum containing nicotine was administered in first-degree relatives of schizophrenia patients who shared the deficit in the P50 gating but were nonsmokers and free of the possible confounds of neuroleptic and anticholinergic medications (Adler et al. 1992). As with the schizophrenia patients, the effect appeared to require a high dose of nicotine. A 2-mg dose of nicotine in chewing gum produced no effect on P50 gating in relatives of schizophrenia subjects. A dose of 6 mg of nicotine was needed to evoke inhibitory mechanisms, suggesting that low-affinity nicotinic receptors are involved in the P50 auditory evoked potential deficit.

The concurrent administration of nicotine and a high-affinity nicotinic receptor antagonist provided further evidence for the role of low-affinity receptors. Most compounds used to differentiate between high- and low-affinity nicotinic receptor types either do not cross the blood-brain barrier or cannot be given to humans. However, the high-affinity-receptor channel blocker mecamylamine crosses the blood-brain barrier and is available as an oral antihypertensive agent. Its antihypertensive activity comes from the blockade of nicotinic cholinergic activation of sympathetic ganglia. High-dose nicotine, administered with mecamylamine, thus activates only the low-affinity receptors, such as α7. When mecamylamine was administered to a first-degree relative of a schizophrenia patient who had the P50 gating deficit, P50 gating was still normalized by nicotine (Freedman et al. 1994).

Nicotinic Receptor Desensitization in Schizophrenia. The corrective effects of nicotine on the P50 auditory sensory gating deficit suggest that self-administration of high doses of nicotine by schizophrenia patients may indeed be an attempt at self-medication. We have also observed a similar corrective effect of cigarettes on deficits in smooth-pursuit eye movements, another trait associated with the genetic risk for schizophrenia (Olincy et al. 1996). There is some evidence that cigarettes influence the course of schizophrenia; several studies have reported that schizophrenia symptoms increase when cigarette consumption decreases (Greenman et al. 1991; Hamera et al. 1995). However, nicotine does not appear to have a long-lasting therapeutic effect on schizophrenia symptoms. The lack of a significant therapeutic effect is consistent with the data from the P50 gating experiments, which show that the effect of nicotine is quite transient. There are two possible mechanisms for this decrease in effect: desensitization of the nicotinic cholinergic receptors or rapid metabolism of nicotine. If rapid metabolism were responsible for the decrease in effectiveness over time, then repeated administration, as exhibited in schizophrenia patients' smoking patterns, would counteract the effect of rapid metabolism and produce longer-lasting improvement. Although patients smoke repetitively, the effect of nicotine appears to diminish, a pattern that suggests that desensitization indeed occurs. The most rapid desensitization rate in the nicotinic receptor family are the α7-nicotinic receptors (Schoepfer et al. 1990; see also figure 3).

If desensitization were responsible for the rapid termination of the effects of the nicotine, then nicotine transdermal patches and other sustained-release formulations would also be ineffective, as sustained release of nicotine promotes desensitization. Anecdotal reports suggest that the nicotine transdermal patch is ineffective for schizophrenia patients (Jenkusky 1993). If desensitization of α7 receptors were a critical pathophysiological factor in schizophrenia, then this process might also affect the response of patients' receptors to the endogenous ligand acetylcholine. Cholinergic neurotransmission changes markedly during different stages of waking and sleep, so observation of P50 gating after various stages of sleep

Figure 3. The cycle of activation, channel opening, desensitization, and resensitization of the pentameric α7-nicotinic cholinergic receptor



Activation by two molecules of acetylcholine or nicotine (represented by black dots) opens the channel to calcium ions and other cations. Influx of these cations through the channel excites the neuron. Then the channel closes, but these agonists stay bound to the receptor so that it is desensitized; that is, it is closed and cannot be activated. Resensitization of the receptor by dissociation of the bound agonists is the slowest of the transitions, so that a small population of receptors may become totally desensitized because the kinetic properties of the cycle make desensitization a semistable state.

might provide evidence for the role of desensitization. Cholinergic neurons in the basal forebrain generally cease firing at the initiation of nonrapid eye movement (NREM) or slow-wave sleep, whereas they are tonically active during rapid eye movement (REM) sleep and the waking state (Szymusiak et al. 1991).

We tested the hypothesis that a period of NREM sleep would allow patients' receptors to resensitize, because cholinergic neurotransmission temporarily ceases, and that, as cholinergic neurotransmission resumed in the subsequent period of waking, desensitization would recur. After baseline recordings, schizophrenia patients were allowed a 10-minute period free of auditory stimulation, during which they attained 2 to 3 minutes of NREM sleep. They were then awakened and post-sleep recordings were obtained. A transient normalization of P50 gating deficit was observed (Griffith and Freedman 1995). A similar experiment in which the subjects reached REM-stage sleep failed to normalize P50 gating in any of the schizophrenia patients (Griffith et al. 1993). Normal subjects do not experience a similar increase in P50 gating after NREM sleep, a difference that suggests that receptor desensitization is a less prominent factor in their physiology. To determine further if the change in P50 gating after a period of NREM sleep reflects nicotinic receptor desensitization, an experiment was performed to reproduce all the other changes in sleep but to maintain stimulation of the nicotinic receptor. A nicotine transdermal patch was applied before the experiment. Although NREM sleep occurred, the P50 auditory evoked potential failed to normalize (Griffith et al. 1996). Therefore, if the cholinergic input is temporarily halted, receptors can be resensitized, and schizophrenia patients can temporarily gate the response to auditory stimuli. Thus, nicotine, which can transiently improve gating of response to auditory stimuli, also causes loss of such gating by desensitizing the receptors.

Such dual effects of cholinergic stimulation are also found in another nicotinic-receptor-based illness, myasthenia gravis, which is characterized by loss of nicotinic receptors at the neuromuscular junction. Myasthenia gravis patients demonstrate increased muscle strength after treatment with the anticholinesterase neostigmine, which increases acetylcholine in the synaptic cleft to activate more post-synaptic nicotinic receptors. This intervention is only a limited treatment for the illness, because all the receptors soon become desensitized, leading to a cholinergic crisis. The loss of receptors in myasthenia gravis results in too few receptors available in a nondesensitized state to support neurotransmission for long periods of time. Sensory gating deficits in schizophrenia may reflect a similar mechanism. The relative deficiency of nicotinic receptors found in postmortem schizophrenic brains may thus explain why desensitization is so problematic (Freedman et al. 1995). Desensitization of nicotinic receptors may have other deleterious effects on brain function, in addition to the loss of sensory gating. The subfornical organ, which samples cerebrospinal fluid osmolality and regulates water drinking, is rich in nicotinic receptors (Härfstrand et al. 1988). Self-induced water intoxication has been related to heavy smoking in schizophrenia patients (Kirch et al. 1985). This life-threatening condition may thus be caused in part by desensitization of critical nicotinic receptors.

Nicotinic Receptors as Therapeutic Targets in Psychosis. Problems with desensitization may limit the effectiveness of currently available nicotinic agonists in schizophrenia, although the development of agents with less marked desensitization properties may be possible. A nicotinic agonist therapeutic strategy may be more immediately helpful for psychoses in which the α7-nicotinic receptor appears to be intact. For example, another psychotic disorder thought to involve cholinergic neurotransmission is Alzheimer's disease. The anticholinesterase physostigmine has had more therapeutic success as an antipsychotic treatment in Alzheimer's than in schizophrenia (Cummings et al. 1993). In Alzheimer's, α-bungarotoxin binding in the brain is intact (Lang and Henke 1983). The principal pathology is thought to be the loss of cholinergic afferent terminals; that is, the α7 receptors are probably normal, but they receive too little acetylcholine. Hence, cholinergic agonist strategies may be particularly helpful for treating this illness.

Nicotinic mechanisms may also be involved in the effects of clozapine in the treatment of schizophrenia. Typical neuroleptics do not affect P50 gating, even if the patient has had a good clinical response; whereas clozapine improves the gating of P50 to normal levels in patients who have a 20 percent improvement in their Brief Psychiatric Rating Scale (Overall and Gorham 1962) scores from their scores while taking typical neuroleptics (Nagamoto et al. 1996). A number of pharmacologic hypotheses have been suggested to explain clozapine's unique therapeutic effect. Hypothesized mechanisms include strong 5-HT_2 serotonergic receptor blockade with relatively weak dopaminergic D_2 receptor blockade, D_4 receptor blockade, and 5-HT_3 receptor blockade (Brunello et al. 1995). The 5-HT_3 receptors are found on cholinergic neurons, where they have an inhibitory effect on the release of acetylcholine. Blockade of 5-HT_3 receptors by clozapine might increase acetylcholine release and, therefore, activation of these nicotinic receptors, which would enhance gating of auditory response. Another possibility is that serotonin inhibits hippocampal and other cerebral interneurons that are excited by acetylcholine, so that

serotonergic blockade could compensate for the loss of nicotinic receptor activation (Oleskevich and Lacaille 1992). Possible corroborating evidence for the hypothesis that clozapine affects the same neuronal systems as nicotine is the finding that schizophrenia patients decrease their cigarette smoking during clozapine administration (McEvoy et al. 1994). Thus, the neurobiology of the interneurons that are a principal target for cholinergic innervation may reveal a variety of mechanisms for the pathogenesis of psychosis and its treatment.

Role of the α7-Nicotinic Receptor in Cellular Growth and Development

Theories of schizophrenia based on the action of a single neurotransmitter often seem to compete with theories based on a deficit in brain growth and development. However, the α7-nicotinic receptor may have a role in growth and development that would allow it to influence this aspect of the pathogenesis of schizophrenia as well (Couturier et al. 1990). In cultured neuroblasts, nicotinic agonists cause retraction of processes; that is, they de-differentiate the neuroblasts. This effect is blocked by α-bungarotoxin, suggesting that an α7 receptor is involved in the regulation of neuronal differentiation (Chan and Quik 1993; Pugh and Berg 1994). The α7 receptors admit calcium into neurons through their ion channels in amounts greater than the *N*-methyl-D-aspartate receptor allows, an activity that has been proposed to have not only longer duration of excitatory action, but also some significance for cell differentiation (Vijayaraghavan et al. 1992). In the intact brain, α-bungarotoxin sensitive receptors are expressed at much higher levels in neonatal animals than in adults and appear in neocortical areas, just as they receive their afferent innervation from the thalamus (Fuchs 1989). It has been suggested that α7-nicotinic receptors, which appear to be expressed in cortical neurons as part of the response to afferent innervation, help form a functional linkage between these neurons and thalamic and basal forebrain cholinergic afferents (Broide et al. 1996). This regulation of the development of afferent innervation may occur in limbic areas as well. For example, inbred mouse strains deficient in α7 receptors also have diminished mossy fiber terminal arborization in the CA3 layer (Stevens et al. 1996). Neurotrophin expression, such as nerve growth factor and its family members, also persists in the hippocampus into adult life and continues to be regulated by α-bungarotoxin-sensitive receptors (Freedman et al. 1993). Thus, a deficit in α7-nicotinic receptors might play a role in the growth and development of the nervous system in addition to their role in altered sensory processing.

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Acknowledgments

This work was supported by the Department of Veterans Affairs Medical Research Service, the National Alliance for Research on Schizophrenia and Depression, and USPHS grants MH-38321, MH-42643, MH-44212, MH-00728, and RR-00051. Dr. Roberta Payne edited the manuscript. Dr. R.L. Bayles made helpful suggestions on the role of sensory gating mechanisms in information processing.

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