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REVIEW

Role of Tegmental Cholinergic Neurons in Dopaminergic Activation, Antimuscarinic Psychosis and Schizophrenia

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Cholinergic neurons of the pedunculopontine nucleus (Ch5) and laterodorsal tegmental nucleus (Ch6) monosynaptically activate dopamine neurons of the substantia nigra, zona compacta (A9), and ventral tegmental area (A10) via muscarinic and nicotinic receptors. Ch5 cells and Ch6 cells are inhibited by local injections of muscarinic agonists, suggesting the presence of autoreceptors. This review advances the hypothesis that the psychotogenic effects of antimuscarinics are triggered by disinhibition of Ch5 and Ch6 cells via their autoreceptors, and that these effects are distinct from the memory-blocking effects of antimuscarinics mediated through the Ch1–Ch4 projections to the forebrain. Neuroleptic and antiparkinson agents with antimuscarinic effects selectively block m1 muscarinic receptors, whereas psychotogenic antimuscarinics are nonselective. In rats, scopolamine injected near Ch5 cells facilitates rewarding brain stimulation and induces locomotion and stereotypy, apparently via activation of dopaminergic systems. Systemically administered scopolamine induces locomotion and stereotypy via muscarinic receptors near Ch5 cells. Ch5 activation and Ch6 activation may be a causal factor in some forms of schizophrenia. Some schizophrenics show early-onset REM sleep, a condition that can result from Ch5 and Ch6 cholinergic activation of the pontine reticular formation. Schizophrenics with early-onset REM, or visual hallucinations, show more severe positive symptoms and negative symptoms. Ch5 cells and Ch6 cells have been found in twice-normal numbers in a few brains of schizophrenics. Several genetic and onset factors for schizophrenia that may be linked to Ch5 cells are considered, as well as treatment strategies based on inhibition of Ch5 cells and Ch6 cells, or blockade of their terminals. ***[Neuropsychopharmacology 12:3–16, 1995]***

KEY WORDS: *Cholinergic receptors; Psychoses, substance induced; Schizophrenia; Scopolamine; Dopamine; Reward*

Although overactivation of dopamine systems is believed by many to be important for the expression of positive symptoms of schizophrenia (Mattysse 1973; Seeman et al. 1975; Creese et al. 1976; Seeman 1992), it is not clear how this overactivation occurs, how it lasts so long, or why the overactivation is not corrected by self-regulation of dopamine cells (Meltzer and Stahl 1976; Grace 1991). Although neuroleptics block positive symptoms primarily via D2 receptors, the dopamine hypothesis has difficulty explaining why other symptoms are not blocked by neuroleptics, why the beneficial effects of neuroleptics occur weeks after the onset of treatment, or why neuroleptics are ineffective in many patients. These problems have led many to propose that dopamine neurons may be one output system for more primary neural events (e.g., Freed 1989; Grace 1991), but no compelling candidate for a more primary neural cause has emerged. The goal of this paper is to propose such a candidate.

Recently, cholinergic neurons of the pedunculo-

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pontine nucleus (Ch5) and laterodorsal tegmental nucleus (Ch6) have been shown to monosynaptically contact tegmental dopamine neurons (Bolam et al. 1991), and strongly activate dopamine neurons via muscarinic and nicotinic receptors (Lacey et al. 1991; Calabresi et al. 1989). Cholinergic stimulation of A9 and A10 dopamine cell groups, or of Ch5 and Ch6 cell groups in rats leads to reward facilitation, feeding, locomotion, and stereotypy, behaviors associated with dopaminergic activation with amphetamine (Yeomans et al. 1985, 1993; Winn 1991). This same cholinergic stimulation leads to a massive increase in dopamine efflux in striatum (Blaha and Winn 1993; Blackburn et al. 1994); therefore, activation of tegmental cholinergic neurons could be a direct source of dopaminergic activation.

Because antimuscarinics can induce a form of psychosis in humans and exacerbate schizophrenia, the hypothesis that cholinergic cells of the midbrain and pontine tegmentum are important in the psychotogenic effects of antimuscarinics and in schizophrenia is considered (Yeomans, 1992). Although mesopontine cholinergic alterations are proposed to be important, this is not a "single-transmitter," a "single-cause," or a "single-disease" hypothesis. Alterations of several types in serotonin, norepinephrine, dopamine, glutamate, or acetylcholine-containing cells, for example, could combine to alter the resulting activation in these systems in different schizophrenic populations.

Previous reviews of cholinergic mechanisms in schizophrenia have reached conflicting conclusions. Whereas some have emphasized that antimuscarinics administered systemically can induce positive and negative symptoms that resemble schizophrenia (Abood and Biel 1962; Baumgold et al. 1977; Lowy et al. 1977), others have emphasized the delirium, confusion, and memory loss that differentiate antimuscarinic psychosis and schizophrenia (Meltzer and Stahl 1976; Davis et al. 1978). Singh and Kay (1985) proposed that central cholinergic activity may be reduced in many schizophrenics. Tandon and Greden (1989) concluded that muscarinic hyperactivity leads to negative, not positive, symptoms of schizophrenia. Others have concluded that cholinergic mechanisms are not important to schizophrenia (Davis et al. 1978).

The difficulty in interpreting the effects of systemically administered muscarinics is that there are at least nine central cholinergic cell groups (in addition to motoneurons) and five types of muscarinic receptors:

1. Most interpretations discuss involvement of cholinergic interneurons of the striatum, or basal forebrain cholinergic cells (Ch1–4) that project to the forebrain. Four other projecting cholinergic cell groups (Ch5–8) have recently been described, along with many new anatomical connections (Mesulam et al. 1983; Rye et al. 1987; Woolf 1991).
2. Five types of muscarinic receptors (m1–m5) have been genetically cloned (Kubo et al. 1986; Bonner et al. 1987; Peralta et al. 1987) and localized in the brain in relation to the cholinergic cell groups and their connections (Buckley et al. 1988; Weiner et al. 1990; Vilaro et al. 1990, 1991, 1992).
3. Neuroleptic and antiparkinson agents with an antimuscarinic action have been shown to selectively block the m1 receptor, whereas the antimuscarinics that induce or worsen psychosis most potently are nonselective (Bolden et al. 1991).
4. Many cholinergic cells have autoreceptors, so that systemically administered drugs can have opposing effects on cholinergic cells or presynaptic terminals versus postsynaptic cells.
5. Local injections of muscarinic drugs in animals have identified sites that could mediate the central actions of systemically administered drugs.

Therefore, basic cholinergic mechanisms are reviewed here before addressing the thornier issues of how centrally acting muscarinics might work in human patients.

ANATOMY AND PHYSIOLOGY OF Ch5 NEURONS AND Ch6 NEURONS

Mesopontine cholinergic cells are located in a roughly continuous longitudinal band stretching from the caudal end of the substantia nigra to the floor of the fourth ventricle in rats, cats, and humans (Rye et al. 1987; Mesulam et al. 1989; Woolf 1991). The Ch5 cell group is located diffusely within and around the pedunculopontine tegmental nucleus (PPT). The Ch6 cell group is densely clustered in and around the laterodorsal tegmental nucleus (LDT) of the pons.

Ch5 and Ch6 cholinergic cells have widespread, overlapping projections. The heaviest projections are to the thalamus, to virtually all thalamic nuclei, but there are projections to the reticular formation, locus coeruleus, dorsal raphe, ventral tegmental area (VTA), substantia nigra, zona compacta, lateral hypothalamus, basal forebrain nuclei, and limbic frontal cortex, among others (Woolf 1991) (Figure 1).

Ch5 and Ch6 cells provide the only known cholinergic inputs to VTA and substantia nigra. Early doubts about these connections (e.g., Sugimoto and Hattori 1984; Rye et al. 1987) have been resolved by several recent studies (Clarke et al. 1987; Gould et al. 1989; Cornwall et al. 1990; Fujimoto et al. 1990; Woolf et al. 1990; Bolam et al. 1991). The lateral parts of substantia nigra receive projections mainly from more lateral Ch5 cells, whereas the medial substantia nigra and VTA appear to receive projections from medial Ch5 and from Ch6 cells (Jackson and Crossman 1983; Gould et al. 1989; Cornwall et al. 1990).

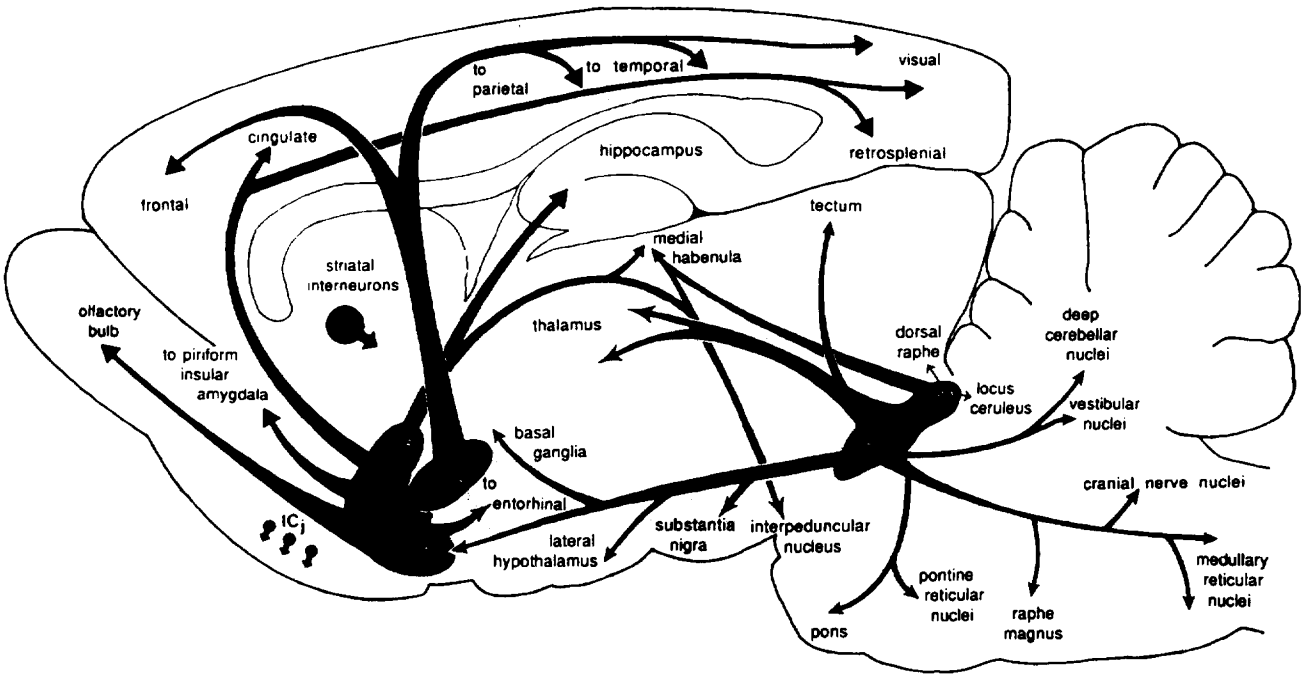

Figure 1. Schematic overview of cholinergic cell groups and projections. The entire cortical mantle is innervated by the basal forebrain subsystem (Ch1–Ch4) and the subcortical mass is innervated by the mesopontine subsystem (Ch5–Ch6). Minor cell groups in the habenula (Ch7) and parabigeminal nucleus (Ch8) are not shown (from Woolf 1991).

Near dopamine cells, low to moderate densities of nicotinic and muscarinic receptors are found in the rat brain and in the human brain (e.g., Cortes et al. 1984; Mash and Potter 1986). Selective lesions of these dopamine cells with 6-hydroxydopamine result in loss of both nicotinic and muscarinic receptors in rats (Clarke and Pert 1985; Vilaro et al. 1990), suggesting that both receptor classes are found only on the dopamine cells, or on terminals that require the presence of dopamine cells. High concentrations of acetylcholinesterase (AChE) are found in and around dopamine cells (Butcher and Woolf 1982; Greenfield 1991). ChAT-labelled terminals are found in substantia nigra, pars compacta, in low to moderate densities (Gould et al. 1989; Bolam et al. 1991), and these terminals make multiple asymmetric contacts onto the dendrites of dopamine cells (Bolam et al. 1991). The density of ChAT-labeled varicosities is higher in the VTA of humans than in the substantia nigra (Mesulam et al. 1992).

Cholinergic agonists nicotine, or muscarine directly activate VTA, or nigral dopamine cells recorded in rat midbrain slices (Calabresi et al. 1989; Lacey et al. 1991). The muscarinic actions were longer in duration, and more reliable on repeated tests than the nicotinic actions. There was no evidence of depolarization block or burst firing. In intact rats, carbachol or nicotine stimulation of the substantia nigra induced dopamine release in the striatum, measured by voltammetry (Blaha and Winn 1993). Together these results indicate powerful and reliable activation of A9 dopamine cells and A10 dopamine cells by monosynaptic connections from Ch5 cholinergic cells and Ch6 cholinergic cells.

About 70% of synapses onto dopamine cells are symmetric GABAergic inhibitory synapses (Bolam et al. 1991). Of the chemically characterized asymmetric contacts, only acetylcholine and excitatory amino acids strongly excite dopamine neurons (Kalivas 1993). Cholinergic agonists induce a steady increase in firing, but glutamate induces oscillatory burst firing (Lacey et al. 1991; Johnson et al. 1992). 5HT-containing asymmetric contacts onto dopamine cells have mixed effects, but 5HT effects on cholinergic inputs appear to be inhibitory; 5HT causes Ca^{++} to enter the dendrites of tegmental dopamine cells (Nedergaard et al. 1988), which leads to the release of dopamine and AChE from the dendrites (Llinas et al. 1984; Greenfield 1991). Therefore, 5HT can reduce cholinergic activation of dopamine cells by:

1. Dendritic release of dopamine, which then inhibits neighboring dopamine cells through autoreceptors.
2. Rapid enzymatic breakdown of acetylcholine released from cholinergic terminals.
3. Direct inhibition of Ch5 cholinergic cells and Ch6

cholinergic cells, via raphe projections to these cholinergic cells (Luebke et al. 1992a; Semba and Fibiger 1992).

Behaviors Induced by Cholinergic Stimulation of Dopamine and Ch5 Cells in Rats

Cholinergic agonists injected near dopamine cells facilitate behaviors associated with dopamine stimulation. Carbachol (1 μg to 3 μg) injections into the VTA were rewarding to rats on a conditioned place preference task (Yeomans et al. 1985). Carbachol increased feeding when injected into the nigra (Parker et al. 1991; Winn 1991). Nicotine or cytisine increased locomotion when injected into the VTA (Reavill and Stolerman 1990).

Cholinergic blockers, atropine, scopolamine, or hemicholinium injected into VTA strongly inhibited brain-stimulation reward for electrodes placed in the hypothalamus, midbrain or pons (Yeomans et al. 1985; Kofman and Yeomans 1989; Kofman et al. 1990). The inhibitory effect of atropine was dose-dependent (10 μg to 60 μg), repeatable on subsequent days, and recovered gradually over a period of 2 hours. Preinjections of carbachol prevented the atropine blockade of brain-stimulation reward, suggesting that the atropine effect is mediated via muscarinic receptors (Kofman et al. 1990). This atropine inhibition of reward was not accompanied by motor debilitation.

Injections of muscarinic agents near Ch5 cells in PPT produced the opposite effects. Carbachol blocked brain-stimulation reward and reduced locomotor activity, whereas scopolamine (100 μg) strongly facilitated brain-stimulation reward and increased locomotor activity and stereotypical responses (Mathur and Yeomans 1993; Yeomans et al. 1993). These suggest that Ch5 cells are inhibited or disinhibited via "somatodendritic autoreceptors." Consistent with this idea, scopolamine injections into PPT increased dopamine efflux in the striatum (Blackburn et al. 1994).

The connections of Ch5 cells to dopamine cells may also be critical for drug rewards. Bilateral excitotoxic lesions of PPT blocked conditioned place preferences for opiate and stimulant drugs (Bechara and van der Kooy 1989, 1992; Bechara et al. 1992). Lesions of VTA dopamine cells with 6-OHDA blocked the self-administration of nicotine (Corrigall et al. 1992). Therefore, cholinergic activation of A9 and A10 dopamine cells by Ch5 and Ch6 inputs appears important for a variety of dopamine-related functions including reward, feeding, hyperactivity, and stereotypy. In particular, scopolamine in PPT induces stereotypy, locomotion, and facilitation of brain-stimulation reward; phenomena that are similar to those produced by amphetamine injected systemically or in dopamine terminal areas.

Ch5 autoreceptors appear to be important in mediating the behavioral effects of systemically administered anticholinergics. Scopolamine (1 mg/kg to 10 mg/kg) induces stereotypy and hyperactivity in rats (Arnfred and Randrup 1968; Shannon and Peters 1990), as well as dopamine release in the striatum (Blackburn et al. 1994). Carbachol preinjections in PPT reduced both the stereotypy and locomotion produced by systemic scopolamine (Yeomans et al. 1994). The carbachol-induced inhibition was not observed if the carbachol injections in PPT followed the systemic scopolamine injections suggesting competition for muscarinic receptors in PPT. Therefore, systemic scopolamine appears to act via mesopontine muscarinic autoreceptors rather than forebrain receptors.

ANTIMUSCARINIC PSYCHOSIS

Many antimuscarinic agents that cross the blood-brain barrier, including atropine, scopolamine, quinuclidinyl benzilate (QNB), Ditran, and other piperidyl glycolates can at high doses evoke a psychotic state that includes tactile, visual, auditory and olfactory hallucinations, hyperactivity, severe disruption of thinking, including memory loss and confusion, as well as peripheral antimuscarinic effects and hyperthermia (Abood and Biel 1962; Grancher and Baldessarini 1975; Mego et al. 1988; Fischer 1991). The visual hallucinations can involve clearly defined objects such as people and animals and are often colorful. The auditory hallucinations can involve music or voices with subjects sometimes carrying on long conversations with these voices.

At low doses, subjects have difficulty sustaining attention, but can accurately describe their hallucinations and delusions which resemble those of endogenous schizophrenia (Abood and Biel 1962; Wilson and Shagass 1964; Singh and Kay 1985). The next day there is good recall of these experiences. At higher doses the subjects lose the ability to reason clearly and then to distinguish fantasy from reality, and eventually become incoherent (Meduna and Abood 1959; Fischer 1991).

Elderly people and those with a history of psychosis appear to be most susceptible to antimuscarinic psychosis (Mego et al. 1988; Ziskind 1988; Farley 1992). Several reports describe psychosis in elderly people who overused transdermal ear patches containing scopolamine as an antidote against nausea or motion sickness. Schizophrenics who take massive doses of antiparkinson drugs, especially trihexiphenidyl are also susceptible (Smith 1980; Fisch 1987).

By comparison, amphetamine psychosis also can produce florid auditory, olfactory, tactile and visual hallucinations, but there is less thought disorganization, difficulty in sustaining attention and delirium than with antimuscarinic psychosis (Snyder 1973). With amphetamine psychosis, the cardinal characteristic is paranoia.

Confusion, memory loss, and peripheral side effects are diagnostic for "toxic cholinergic syndrome."

In some cases of antimuscarinic psychosis, delusions and hallucinations occur without delirium, confusion or memory loss (Meduna and Abood 1959; Fisher 1991); therefore, confusion and memory loss can be thought of as additional features of antimuscarinic psychosis that are not necessarily linked to the delusions and hallucinations.

PROPOSED MECHANISMS OF ANTIMUSCARINIC PSYCHOSIS

Antimuscarinic psychotogens are all nonspecific in their actions. For example, they block all five muscarinic receptor types, m1 to m5, effectively (Table 1). By contrast, neuroleptics with antimuscarinic effects and antiparkinson antimuscarinics induce or worsen psychosis only at much higher doses (Singh and Kay 1985; El-Yousef et al. 1973). Neuroleptics and antiparkinson drugs are all highly selective m1 (and sometimes m4) blockers (Table 1), which accounts for their therapeutic advantage. The psychotogenic effects of antimuscarinics, therefore, cannot occur primarily via m1 receptors or m4 receptors.

These m1 and m4 receptors are almost entirely localized to the forebrain (Figure 2). In the striatum, muscarinic receptors are primarily m1 receptors and m4 receptors, with m2 receptors found on the cholinergic interneurons as autoreceptors (Vilaro et al. 1991; Bernard et al. 1992). This suggests that antiparkinson antimuscarinics act primarily on the forebrain with the striatum a likely target. The muscarinic receptors on dopamine cells are exclusively of the m5 type (Vilaro et al. 1990); therefore, if antimuscarinics produced psychosis by blocking m5 receptors, the effect of muscarine on dopamine cells should be inhibitory. Because the effect of muscarine on dopamine cells is clearly excitatory (Lacey et al. 1991), m5 receptors are also unlikely to be the site of psychotogenic action; therefore, m2 receptors and m3 receptors are the remaining candidates.

About 70% of muscarinic receptors in brainstem, including PPT and LDT, are of the m2 type (Li et al. 1991; Vilaro et al. 1992) with low quantities of other receptors (Vilaro et al. 1991; Wall et al. 1991a,b). The

Table 1. Binding (Kd) of Various Antimuscarinic Agents with Genetically Cloned Human Muscarinic Receptors (m1–m5).

		Human Muscarinic Subtype (Mean Kd ± SEM in nM)				
	m2/m1	m1	m2	m3	m4	m5
Psychotogens with anti-muscarinic actions						
QNB	0.77	0.035 ± 0.002	0.027 ± 0.002	0.088 ± 0.003	0.034 ± 0.002	0.043 ± 0.003
Atropine	1.8	0.50 ± 0.03	0.90 ± 0.03	1.1 ± 0.2	0.6 ± 0.1	1.7 ± 0.1
Scopolamine	1.8	1.1 ± 0.2	2.0 ± 0.1	0.44 ± 0.01	0.8 ± 0.2	2.07 ± 0.01
Antiparkinsonians with antimuscarinic actions						
Benztropine	6.1	0.231 ± 0.005	1.4 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	2.8 ± 0.1
Biperiden	13.1	0.48 ± 0.02	6.3 ± 0.5	3.9 ± 0.1	2.4 ± 0.3	6.3 ± 0.1
Trihexyphenidyl	4.4	1.6 ± 0.2	7 ± 1	6.4 ± 0.4	2.6 ± 0.4	15.9 ± 0.1
Procyclidine	5.4	4.6 ± 0.7	25 ± 2	12.4 ± 0.4	7 ± 1	24 ± 1
Neuroleptics with anti-muscarinic actions (A = atypical)						
Thioridazine	5.2	2.7 ± 0.3	14 ± 3	15 ± 1	9 ± 1	13 ± 1
Clozapine (A)	15.5	3.1 ± 0.7	48 ± 1	20 ± 1	11 ± 1	11.2 ± 0.4
Fluperlapine (A)	8.1	8.8 ± 0.2	71 ± 2	41 ± 6	14 ± 2	17 ± 1
Mesoridazine	1.5	10 ± 1	15 ± 3	90 ± 2	19 ± 2	60 ± 10
Chlorprothixene	2.5	11 ± 1	28 ± 3	22 ± 1	18 ± 2	25 ± 1
Zotepine (A)	7.8	18 ± 6	140 ± 14	73 ± 4	77 ± 4	260 ± 20
Chlorpromazine	6.0	25 ± 3	150 ± 14	67 ± 4	40 ± 3	42 ± 2
Loxapine	4.7	63.9 ± 0.9	300 ± 100	390 ± 45	300 ± 20	241 ± 8
Prototypic M1 selective antimuscarinic						
Pirenzepine	33.8	8 ± 1	270 ± 10	150 ± 10	28 ± 1	170 ± 10

Psychotogenic antimuscarinics are all non-selective. Antiparkinsonian and neuroleptic agents with muscarinic binding are all m1 selective, with a secondary m4 selectivity. (Based on Bolden et al., 1991)

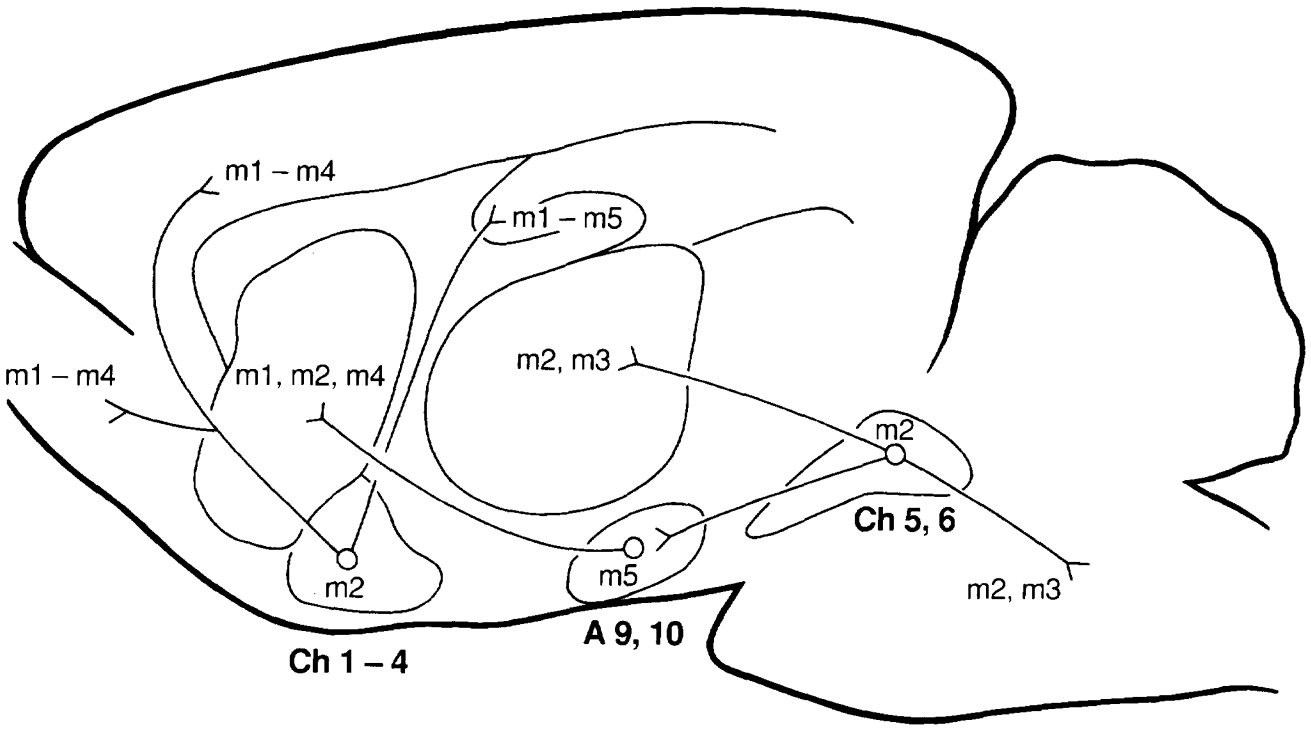

Figure 2. Distribution of genetically cloned muscarinic receptor types (m1–m5), schematically shown in relationship to major cholinergic (Ch1–Ch4, Ch5–Ch6) and dopaminergic (A9–A10) projections. Original figure based on data from Vilaro et al. 1990, 1991, 1992; Weiner et al. 1990; Li et al. 1991; Wall et al. 1991, 1992.

autoreceptors on Ch5 cells and Ch6 cells are likely to be of the m2 type (Leonard and Llinas 1988; Luebke et al. 1992b; Vilaro et al. 1992) as they are in striatum and cortex (Lapchak et al. 1989; Bernard et al. 1992).

The ability of systemic antimuscarinics to induce psychosis in humans is closely related to their ability to induce hyperactivity and behavioral disturbance in rats (Abood and Biel 1962; Baumgold et al. 1977). As discussed previously, hyperactivity and stereotypy induced by systemic scopolamine in rats is mediated mainly via muscarinic receptors near PPT (Yeomans et al. 1994). This suggests that the ability of antimuscarinics to induce psychosis is associated with their ability to block autoreceptors in PPT. It is proposed, therefore, that antimuscarinic psychosis (not including the memory loss) in humans results from the blockade of mesopontine autoreceptors.

Ch5 cells and Ch6 cells project heavily to the thalamus, diffusely activating these thalamic systems (Steriade et al. 1990). Muscarinic activation of thalamus in turn induces diffuse cortical activation and EEG desynchronization, and is believed to result in poor sensory filtering. Therefore, diffuse thalamic activation by Ch5 systems and Ch6 systems may worsen the confusion and inability to inhibit thoughts or external stimuli in antimuscarinic psychosis.

The memory inhibiting effects of antimuscarinics have been associated with blockade of Ch1-4 cholinergic projections to the cerebral cortex (Bartus et al. 1982; Coyle et al. 1983). Therefore, the delirium and memory loss observed during antimuscarinic psychosis may depend upon the sensitivity of cortical cholinergic systems (Ch1-4), whereas the delusions and hallucinations may be associated with brain stem cholinergic systems (Ch5, Ch6).

In conclusion, it is proposed that the psychotogenic actions of antimuscarinics occur via m2 autoreceptors on the Ch5 cholinergic cells and Ch6 cholinergic cells, whereas the antiparkinson effects and memory deficits occur via m1 receptors in the forebrain.

Ch5 AND Ch6 CELLS AND SCHIZOPHRENIA

Could activation of Ch5 cells and Ch6 cells be a route for the induction or exacerbation of schizophrenia? Links between these cells and some types of schizophrenia are found in studies of REM sleep, postmortem brains, drug abuse, and symptom severity in schizophrenics.

REM SLEEP IN SCHIZOPHRENICS

The similarity of dreams and schizophrenic hallucinations has interested many psychiatrists (e.g., Gillin and

Wyatt 1975), but objective evidence for this link has been difficult to obtain. EEG studies show that most parameters of sleep are normal in schizophrenics. The most consistent difference (in inconsistent literature) is decreased mean REM latency in schizophrenics versus normals (Feinberg and Hiatt 1978; Keshevan et al. 1990; Tandon et al. 1992), but decreased delta wave amplitude and duration has also been observed in several studies (Caldwell 1969; Feinberg and Hiatt 1978). Although most schizophrenics are normal in REM latency, 10% to 30% of schizophrenics have sleep-onset REM (i.e., REM in first 15 minutes of sleep), a condition rarely observed in normals (Taylor et al. 1991). The exceptional schizophrenics, therefore, account for most of the small mean difference.

Schizophrenics with early-onset REM tend to have severe symptoms, both positive and negative (Tandon et al. 1992). When all schizophrenic subjects were included together, REM latency correlated with both negative symptom severity ($r = -0.52$) and with positive symptom severity ($r = -0.41$). When the groups were analyzed, the correlations were higher for previously drug-treated schizophrenics, but were insignificant for untreated schizophrenics. It is possible that severe schizophrenics are more likely to have had previous drug treatment, although the alternative hypothesis that the neuroleptics caused the REM changes is not excluded.

Although REM latency is also reduced in depressives, the pattern of sleep changes in depressives is different than in schizophrenics (Gillin et al. 1979; Tandon et al. 1992). In schizophrenics, the REM latency was not related to the severity of additional depressive symptoms, therefore, the mean REM latency change was not simply the result of concurrent depressive symptoms (Keshevan et al. 1990; Tandon et al. 1992).

REM onset can be initiated by cholinergic activation of the pontine reticular formation by Ch5 cells and Ch6 cells. Cholinergic agonists microinjected into the dorsocaudal pontine reticular formation of cats induce pontine-geniculate–occipital waves and REM onset (Katayama et al. 1986; Callaway et al. 1987). Spontaneous REM is blocked by muscarinic blockers in the same sites (Baghdoyan et al. 1984; Shiromani and Fishbein 1986). The cholinergic input to this pontine reticular formation area comes from Ch5 cells and Ch6 cells (Mitani et al. 1988; Shiromani et al. 1988). Lesions of Ch5 cells and Ch6 cells block REM sleep in cats (Webster and Jones 1988). Studies of peripheral cholinergic manipulations in humans have been interpreted as support for this model (Sitaram et al. 1978). In schizophrenics, administration of the cholinergic agonist RS86 shortens REM latency and increases REM density (Riemann et al. 1991). Therefore, severe schizophrenia appears to be associated with early-onset REM sleep, a condition that can result from cholinergic activation of the pontine reticular formation from Ch5 cells and Ch6 cells.

POST MORTEM STUDIES

There is substantial evidence that Ch5 cells are lost in Parkinson's disease and progressive supernuclear palsy (PSP). NADPHd-containing, that is, cholinergic (Vincent et al. 1983) cells in lateral PPT were decreased by about 40% in Parkinson's patients versus age-matched controls (Hirsch et al. 1987; Jellinger 1988). The loss was about 65% for PSP (Hirsch et al. 1987; Zweig et al. 1987), a disease that shares many symptoms with Parkinson's disease.

There is some evidence that Ch5 cell and Ch6 cell counts are increased in schizophrenia. Karson et al. (1991) discovered that NADPHd-containing cells were about twice as common in the PPT nuclei and LDT nuclei of four brains of schizophrenics as in five control brains (two alcoholics, one depressed, and two normals). The small standard errors in the control group, and the large standard errors in the schizophrenic group, imply that two of the brains from schizophrenics had much more than twice as many Ch5 cells and Ch6 cells. No difference was found in these brains in the number of neurons in the nearby locus coeruleus where noradrenergic neurons also show NADPHd. Recently, the sample size has been increased to nine brains of schizophrenics, with a mean increase of 60% in Ch5 cells and Ch6 cells versus normals (Garcia-Rill personal communication).

Because cell number is usually determined before birth, Ch5 cells and Ch6 cells may be overproduced prenatally in these schizophrenics. This hypothesis is difficult to test, however, because schizophrenia cannot be diagnosed prenatally. If so, the increased number of NADPHd-containing cells could be a predisposing, genetically determined factor in some schizophrenics. Whether or how increased numbers of cholinergic cells might predispose to schizophrenia is not known.

Cholinergic enzyme estimates have been inconsistent (Singh and Kay 1985). McGeer and McGeer (1977) found higher overall levels of ChAT and AChE in the brains of schizophrenics than in the brains of controls, but Domino et al. (1973) found no difference. Both increased and decreased levels of ChAT and AChE have been reported in limbic structures, such as the septum, hippocampus, amygdala, and nucleus accumbens (Domino et al. 1973; Wise et al. 1974; Bird et al. 1977; McGeer and McGeer 1977). Of interest to the Ch5 hypothesis, McGeer and McGeer (1977) found AChE levels significantly increased over normals in four thalamic nuclei, all of which receive their cholinergic input from

the Ch5 cell groups and Ch6 cell groups; over the entire thalamus, brains from schizophrenics had 53% more AChE.

ABUSE OF CHOLINERGIC DRUGS BY SCHIZOPHRENICS

Some schizophrenics self-administer high doses of antimuscarinic agents, especially trihexyphenidyl (Smith 1980; Fisch 1987). Schizophrenics smoke cigarettes at an unusually high rate (90% of schizophrenics, 33% of normals, 45% to 70% of other psychotics) which may indicate an increased tendency to self-administer nicotine (Hughes et al. 1986; Lohr and Flynn 1992). From the animal studies reviewed previously, one could speculate that the rewarding effects of nicotine occur through nicotinic receptors on dopamine cells, whereas the rewarding effects of antimuscarinics occur through muscarinic autoreceptors.

ANTIMUSCARINICS AND SCHIZOPHRENIA

When nonselective antimuscarinics are given to chronic schizophrenics, both positive and negative symptoms are exacerbated (Gershon and Olariu 1960; Tourlentes et al. 1960; El-Yousef et al. 1973; Singh and Smith 1973; Singh and Kay 1975). These symptoms were reported to resemble "true" schizophrenia better than acute antimuscarinic psychosis in normals (Gershon and Olariu 1960; Singh and Kay 1985), sometimes producing symptoms that were previously described at the onset of the illness (Gershon and Olariu 1960; El-Yousef et al. 1973). The psychosis could be induced or worsened in schizophrenics repeatedly with repeated administrations (Gershon and Olariu 1960), again suggesting the potential for chronic maintenance of the disease via cholinergic activation. The effects of lower clinical doses of antiparkinson antimuscarinics on schizophrenia appear to be weaker, however, especially on negative symptoms (Singh et al. 1987; Tandon et al. 1991).

Antimuscarinic psychosis at high doses usually involves a predominance of visual hallucinations, whereas schizophrenia usually involves a predominance of auditory hallucinations. Reevaluations of hallucinations in schizophrenia suggest that there is a higher prevalence of visual hallucinations than had previously been suspected (Goodwin et al. 1971; Bracha et al. 1989; Mueser et al. 1990). Although auditory hallucinations were associated with earlier onset of schizophrenia, visual hallucinations were the only hallucinations associated with global severity (Mueser et al. 1990). The high percentage of visual hallucinations (56% of subjects) reported by Bracha et al. (1989) was attributed to the severity of schizophrenia in the patients at the NIMH research wards.

Schizophrenics with intense mesopontine cholinergic involvement may be a subpopulation, i.e. those showing severe global symptoms, disorganized thinking, visual hallucinations, and/or early-onset REM sleep. When activation of mesopontine cholinergic neurons is more gradual, weaker, or earlier in onset than with antimuscarinic psychosis, weaker positive symptoms and negative symptoms may result, involving more auditory hallucinations. Alternatively, mesopontine cholinergic activation may be only one contributing factor in the constellation of factors that lead to schizophrenia.

Differential responses to cholinergic drugs may also be useful in categorizing schizophrenics with cholinergic involvement. As mentioned previously, they are more inclined to self-administer nicotine (through cigarette smoking) or antimuscarinics. Singh and Kay (1985) concluded that paranoid schizophrenics are less responsive to cholinergic drugs than nonparanoid schizophrenics.

CHOLINERGIC CASCADE

Figure 3 shows a highly speculative proposal for how alterations in mesolimbic cholinergic neurons might lead to schizophrenia. Predisposing genetic factors could lead to (1) increased Ch5 cells and Ch6 cells, (2) too few or nonfunctional m2 autoreceptors on Ch5 cells and Ch6 cells, or (3) oversensitive long-term potentiation mechanisms on Ch5 cells and Ch6 cells.

The susceptibility to schizophrenia is very low in late childhood and increases through early adult years. Feinberg (1982) showed that delta-wave amplitude and duration follow the same developmental time course

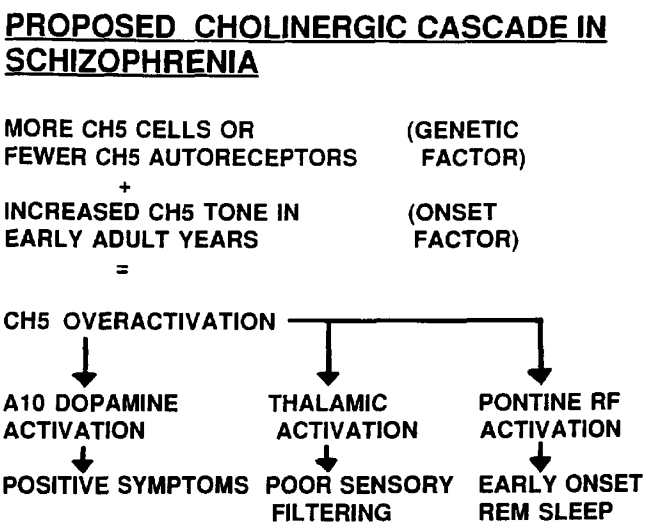

Figure 3. Cascade of events hypothesized to be important in cholinergic-linked schizophrenia.

in normals, being low at birth, increasing in late childhood, then decreasing from ages 12 to 30. Because delta-wave duration and amplitude are greatest in the first sleep cycle immediately before the first REM onset, this may indicate decreased cholinergic tone in late childhood and increased cholinergic tone in early adulthood in normals. Schizophrenics show either decreased delta-wave amplitude and duration or earlier-onset REM as compared to normal adults in most studies (Caldwell 1969; Feinberg and Hiatt 1978; Tandon et al. 1992); therefore, normal developmental changes in the sensitivity of Ch5 cells and Ch6 cells may make the mesopontine cholinergic systems of predisposed individuals more vulnerable to activation.

Reward systems provide an excitatory input to Ch5 cells. Exposure to rewarding drugs could alter the sensitivity of these cells and increase the likelihood of psychotic episodes being triggered.

Once Ch5 cells and Ch6 cells are chronically activated, overactivation of A10 dopamine cells could lead to increased positive symptoms. At high levels, Ch5 activation and Ch6 activation of the pontine reticular formation could lead to early-onset REM accompanied by visual hallucinations. Diffuse activation of the thalamus by Ch5 cells and Ch6 cells could result in an inability to filter information to be relayed to the cortex (Steriade et al. 1990), and disorganized thoughts.

HYPOTHESES REGARDING THERAPY

The slow onset of neuroleptic efficacy against positive symptoms is a problem for the dopamine hypothesis, because neuroleptics block dopamine-related behaviors and dopamine turnover quickly in animals. In animals pretreated with scopolamine, neuroleptics show reduced ability to block these dopamine-related behaviors, such as hyperactivity, brain-stimulation reward, stereotypy, catalepsy, and rotation (Morpurgo and Theobald 1964; Muller and Seeman 1974; Kelly and Miller 1975; Setler et al. 1976; Stephens and Herberg 1979; Murzi and Herberg 1982). Similarly, treatment with high doses of the antiparkinson antimuscarinic, benztropine, reduced the efficacy of neuroleptics in schizophrenia (Singh and Kay 1975). The strong effects of scopolamine on dopamine release and dopamine-related functions suggest that the peculiar ineffectiveness of neuroleptics following scopolamine pretreatment may result from the action of scopolamine on mesopontine cholinergic cells, thereby reducing the immediate therapeutic advantage of neuroleptics. According to this argument, the slow onset of neuroleptic efficacy may indicate mesopontine cholinergic activation in schizophrenics.

If cholinergic activation is a primary causal factor in some types of schizophrenia, how could cholinergic-linked schizophrenia be treated? The usual treatment for antimuscarinic psychosis is to provide supportive care and to wait out the episode. Anticholinesterase treatment with Tacrine or physostigmine often reduces the severity of symptoms (Abood and Biel 1962; Heiser and Gillin 1971; El-Yousef et al. 1973; Grancher and Baldessarini 1975; Ziskind 1988). In terms of the Ch5, Ch6 hypothesis, anticholinesterase treatment may flood the unblocked autoreceptors with acetylcholine from dendrodendritic contacts, inhibiting the Ch5 cells and Ch6 cells.

Selective m2 muscarinic receptor agonists should inhibit Ch5 cells and Ch6 cells. In schizophrenics, transient improvements in symptoms have been reported with a variety of cholinergic agonists, including arecholine, pilocarpine (Pfeiffer and Jenney 1957), or the anticholinesterase, physostigmine (reviewed by Singh and Kay 1985). Several other studies found no effect or mixed effects, and the therapeutic effects often showed tolerance, therefore, these limited successes should be interpreted with caution. The peripheral and central side effects of m2 agonists and anticholinesterases are strong, limiting the doses that can be used to treat the psychosis.

Nonm2 blockers might block the outputs of mesopontine cholinergic cells. In the 1950s and 1960s, coma-inducing doses of scopolamine (5 mg to 100 mg) and atropine (32 mg to 212 mg) were administered 3 times to 6 times a week to inhibit symptoms of psychosis (reviewed by Singh and Kay 1985). Improvements were found in 58% to 77% of schizophrenics in various categories in a study of several hundred patients (Goldner 1967). According to the Ch5, Ch6 hypothesis, these high, repeated doses might completely block postsynaptic muscarinic receptors, and prevent all cholinergic activation, resulting in a temporary relief of symptoms.

Selective m5 blockers should block the outputs of Ch5 cells and Ch6 cells to dopamine cells, and thereby block positive symptoms with fewer peripheral and central side effects (Yeomans 1992; Brann et al. 1993). In rats, cholinergic blockers in VTA, or medial substantia nigra induce little motor inhibition or turning (Kofman et al. 1991; Winn 1991). The weaknesses of this approach are:

1. The outputs of Ch5 cells and Ch6 cells to basal forebrain, thalamus, and brain stem would not be blocked.
2. The effects on m5 receptors in other brain regions, such as hippocampus are not known.
3. No selective m5 blockers are available.

Noncholinergic inhibitors of Ch5 cells and Ch6 cells are serotonin (Luebke et al. 1992a), norepinephrine (Williams and Reiner 1992), and mu opiates (Serafin et

al. 1990). The specific receptor types should be identified so that selective agents can be used for peripheral administration.

A combined strategy is needed. First, behaviors activated by muscarinic disinhibition of Ch5 cells and Ch6 cells should be challenged by appropriate systemic agents. Second, brain and receptor changes or behaviors that identify cholinergic involvement in psychosis should be further examined to identify which populations might benefit from cholinergic-based treatments. Third, linkage between m2 (7q 35–36) and m5 (15q 26) receptor genes and schizophrenia should be sought (Bonner et al. 1991).

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