Muscarinic Tone Sustains Impulse Flow in the Septohippocampal GABA But Not Cholinergic Pathway: Implications for Learning and Memory

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Systemic infusions of the muscarinic cholinergic receptor antagonists atropine and scopolamine (atrop/scop) produce an amnestic syndrome in humans, subhuman primates, and rodents. In humans, this syndrome may resemble early symptoms of Alzheimer’s disease. Behavioral studies in rats have demonstrated that the medial septum/diagonal band of Broca (MSDB), which sends cholinergic and GABAergic projections to the hippocampus, is a critical locus in mediating the amnestic effects of atrop/scop. The amnestic effects of atrop/scop in the MSDB have been presumed but not proven to be caused by a decrease in hippocampal acetylcholine (ACh) release after blockade of a muscarinic tone in the MSDB. Using electrophysiological recordings and fluorescent-labeling techniques to identify living septohippocampal neurons in rat brain slices, we now report that, contrary to current belief, a blockade of the muscarinic tone in the MSDB does not decrease impulse flow in the septohippocampal cholinergic pathway; instead, it decreases impulse flow in the septohippocampal GABAergic pathway via M3 muscarinic receptors. We also report that the muscarinic tone in the MSDB is maintained by ACh that is released locally, presumably via axon collaterals of septohippocampal cholinergic neurons. As such, cognitive deficits that occur in various neurodegenerative disorders that are associated with a loss or atrophy of septohippocampal cholinergic neurons cannot be attributed solely to a decrease in hippocampal acetylcholine release. An additional, possibly more important, mechanism may be the concurrence of a decrease in septohippocampal GABA release and a subsequent disruption in disinhibitory mechanisms in the hippocampus. Restoration of impulse flow in the septohippocampal GABA pathway, possibly via M3 receptor agonists, may, therefore, be critical for successful treatment of cognitive deficits associated with neurodegenerative disorders such as Alzheimer’s and Parkinson’s disease.

Key words: ß7 rhythm; p75 receptor; neurotrophin; acetylcholine; cognition; neurodegeneration

The importance of cholinergic mechanisms for the maintenance of cognitive functioning is well established, and acetylcholinesterase inhibitors, which increase synaptic acetylcholine (ACh) levels, are the most extensively used therapy for Alzheimer’s disease. In contrast, treatments that oppose cholinergic tone, such as the muscarinic receptor antagonists atropine and scopolamine (atrop/scop), produce an amnestic syndrome in rats (Deutsch and Rocklin, 1967), monkeys (Rupniak et al., 1989), and humans (Bartus, 1978; Rusted and Warburton, 1988). In humans, this syndrome is reminiscent of the dementias associated with Alzheimer’s disease and the alcoholic Korsakoff syndrome (Kopelman and Corn, 1988; Izquierdo, 1989) in which a loss in brain cholinergic neurons occurs. In these and other neurodegenerative disorders such as Parkinson’s disease, Lewy body dementia, and Down syndrome, the loss or atrophy of cholinergic neurons has been especially noted in the nucleus basalis and in the medial septum/diagonal band of Broca (MSDB) (Whitehouse et al., 1982; Mufson et al., 1989; Arendt et al., 1995).

The MSDB, which is the primary source of ACh for the hippocampus, is also a critical locus for the amnestic effects of atrop/scop (Givens and Olton, 1994). Thus, infusions of muscarinic agonists into the MSDB alleviate the learning and memory deficits induced by systemic atrop/scop, whereas intraseptal infusions of atrop/scop strongly mimic the impairments induced by systemic antagonists (Givens and Olton, 1995) and also block the hippocampal ß7 rhythm (see Stewart and Fox, 1990; Givens and Olton, 1994).

Despite its importance, the cellular mechanism(s) underlying the muscarinic tone in the MSDB has never been elucidated. It has, however, been presumed that muscarinic antagonists in the MSDB act by decreasing an excitatory muscarinic tone on septohippocampal cholinergic neurons that would subsequently reduce hippocampal ACh release and, as a consequence, impair performance in learning and memory tasks (Givens and Olton, 1994; Givens and Sarter, 1997). Our recent findings, however, provide strong evidence that septohippocampal cholinergic neurons are actually never excited by muscarinic agonists but are instead inhibited by them (Wu et al., 2000). Theoretically, therefore, if cholinergic neurons were indeed under a muscarinic tone, administration of muscarinic antagonists would increase and not decrease impulse flow in the septohippocampal cholinergic pathway. The increased hippocampal ACh release should then facilitate learning and memory processes. How then do muscarinic receptor antagonists produce amnesia?

A second, very important issue relates to the source of ACh that provides a muscarinic tone in the MSDB. Theoretically, the muscarinic tone in the MSDB could be caused by ACh released via the extrinsic brainstem cholinergic afferents to the MSDB (Woolf and Butcher, 1986) and/or caused by ACh released from within the nucleus via collaterals of septohippocampal cholinergic neurons (Bialowas and Frotscher, 1987; Leranth and Frotscher, 1989). If the muscarinic tone were to be dependent, even in part, on the septohippocampal cholinergic neurons, then it would be compromised in the above-mentioned neurodegenerative disorders in which a loss or atrophy of septohippocampal but not brainstem cholinergic neurons occurs. Thus, the question of the source of the muscarinic tone in the MSDB is of great therapeutic significance. In our previous in vitro studies, we observed that identified septohippocampal cholinergic neurons within the MSDB are spontaneously
firing and thus capable of tonically releasing ACh locally via axon collaterals (Wu et al., 2000). We therefore hypothesized that the cholinergic tone in the MSDB, which is critical to learning and memory in vivo, may, at least in part, be caused by ACh that is released locally by the spontaneously firing septohippocampal cholinergic neurons. The present study was therefore designed to determine the cellular mechanisms underlying the muscarinic tone in the MSDB.

MATERIALS AND METHODS

Slice preparation for electrophysiological recordings. Brain slices containing the MSDB were prepared from young adult Sprague Dawley Sprague Dawley rats (2–4 weeks old) by the use of methods detailed previously (Alreja and Liu, 1996). Briefly, rats were anesthetized with chloral hydrate (400 mg/kg, i.p.) and killed by decapitation. The artificial CSF (ACSF), pH 7.35–7.38, containing ACSF and trimmed to yield a small block containing the MSDB. Coronal slices of 300 μm thickness containing the MSDB were cut with a vibrating knife microtome (Frederick Haer, Brunswick, ME) and transferred to a Plexiglas recording chamber (1.5 ml volume) on the fixed stage of an Olympus BX50WI scope. Sagittal slices were used for extracellular recordings on unidentifiable cells (see above); a slice was kept inibase at 33 ± 0.5°C. One to 2 hr later the slice was used for recording. The chamber was continuously perfused with normal ACSF at a rate of 1–2 ml/min.

Labeling of septohippocampal cholinergic neurons using indocarbocyanine-192IgG. Young adult male Sprague Dawley albino rats (14–21 d old) were anesthetized with the following cocktail: ketamine at 75 mg/kg, xylazine at 4 mg/kg, and acepromazine at 0.075 mg/kg. Indocarbocyanine (Cy3-192IgG) was microinjected bilaterally into the lateral ventricle of each rat with a Hamilton syringe and the brain slices. The threshold of activation and high frequency after and collision of the antidromic spikes with orthodromic spikes (see Fig. 4A,B). Similar criteria have been previously described methods (Alreja and Liu, 1996; Liu et al., 1998; Alreja et al., 2000). The threshold of activation and the latency of antidromic activation were measured for each SHN, and the latency measurement was used to compute the conduction velocity for each SHN. The distance between the stimulating and the recording electrodes was measured by the use of a calibrated graticule located in the eyepiece of the dissection scope.

RESULTS

Muscarinic antagonists inhibit MSDB neurons in vitro

To determine whether the muscarinic tone that is observed in vivo is intrinsic to the MSDB, we tested the effects of the muscarinic receptor antagonists ati scop on septohippocampal neurons in vitro in brain slices. The in vitro slice preparation, although retaining the cell bodies of the septohippocampal cholinergic neurons, is devoid of the brainstem neuronal cholinergic cell bodies that provide extrinsic cholinergic afferents to the MSDB. The presence of a tone in vitro would therefore suggest the involvement of locally released ACh. Several studies have shown that exogenously applied ACh or muscarine can produce both inhibitory and excitatory effects in MSDB neurons, a significant number of which are spontaneously firing (Dutar et al., 1983; Lamour et al., 1984; Segal, 1986; Liu et al., 1998). We therefore speculated that if a muscarinic tone were present in the MSDB in vitro then both applications of ati scop would have an effect opposite to that of the muscarinic agonists; i.e., ati scop would either disinhibit or disfacilitate MSDB neurons, an effect that would be observed as an increase or decrease, respectively, in basal firing rates.

To test the presence of a muscarinic tone in vitro in MSDB neurons, we first performed extracellular recordings on unidentified, spontaneously firing MSDB neurons and tested the effect of bath-applied ACh/muscarine and ati scop on basal firing rates. Of the 36 cells tested with ati scop (100 nM–3 μM; 10–20 min; n = 21 for atropine and n = 15 for scopolamine), 35 neurons were excited by ACh/muscarine, and 1 was inhibited by ACh/muscarine. Interestingly, in 52.8% of the neurons excited by ACh/muscarine (19 of 36), bath-applied ati scop produced a striking reduction or even a complete cessation of basal firing (11 of 19 neurons tested; Fig. 1A, suggesting that a muscarinic tone is indeed present in the MSDB in vitro. Thus, atropine reduced basal firing rates from a mean rate of 4.5 ± 1.5 Hz to a rate of 1 ± 0.3 Hz (n = 9), and scopolamine reduced the baseline firing from 5.6 ± 0.4 to 2 ± 0.37 Hz.
Spontaneously firing cholinergic neurons are present within the MSDB

We next confirmed the presence of spontaneously firing cholinergic neurons within the MSDB in our brain slices because the presence of such neurons would be critical for the generation of a muscarinic tone in vitro. Septohippocampal cholinergic neurons were identified in brain slices either in the living state by using a novel fluorescent marker, Cy3–192IgG, or in the fixed state after completion of the experiment using the technique of double immunolabelling. Cy3–192IgG is a conjugate of the inert fluorochrome Cy3 and of p75 receptor-expressing neurons (Hartig et al., 1998), which in the MSDB are exclusively cholinergic. In a recent study, we confirmed the specificity of Cy3–192IgG and also found that the presence of Cy3–192IgG in living cholinergic neurons alters neither their electrophysiological properties nor their responsivity to muscarinic agonists (Wu et al., 2000).

In brain slices viewed with an IR-DIC microscope equipped for fluorescence, Cy3–192IgG-labeled neurons appeared as red fluorescent neurons with a punctate-type staining (Fig. 2A, left). As noted previously, Cy3–192IgG-labeled neurons had a healthy appearance (Fig. 2A, right), and 55% (39 of 71) of these neurons fired spontaneously (Fig. 2B) at a mean rate of 2.1 ± 0.3 Hz recorded extracellularly. Whole-cell recordings established in 70% of the neurons confirmed the presence of an electrophysiological signature typical of cholinergic neurons (Fig. 2C). In brain slices prepared from un.injected rats, neurons with electrophysiological characteristics of cholinergic neurons (Griffith and Matthews, 1986; Gorelova and Reiner, 1996) also displayed similar spontaneous firing activity (data not shown).

Finally, recordings were also made in brain slices taken from rats in which the inert retrograde tracer rhodamine coated on latex microspheres was injected into the hippocampus 2 d before recording (Fig. 2E). Rhodamine beads label both septohippocampal cholinergic and septohippocampal GABAAergic neurons. After recording of the basal firing rates, rhodamine-labeled cells were impaled and filled with the intracellular marker Lucifer yellow (Fig. 2D, top). Double-labeling studies, using an antibody against ChAT, were used to determine whether the recorded cell was cholinergic. Three of three double-labeled, retrogradely marked septohippocampal cholinergic neurons (Fig. 2D, bottom) also fired spontaneously at a rate of 3.8 ± 2.2 Hz. Thus, spontaneously firing septohippocampal cholinergic neurons, which could theoretically release ACh tonically via axon collaterals, are present within the MSDB.

Muscarinic receptor antagonists inhibit noncholinergic MSDB neurons

Having demonstrated the presence of muscarinic tone in vitro, we next determined the effects of atropine (Atr) on identified septohippocampal cholinergic and septohippocampal noncholinergic neurons. As mentioned above, septohippocampal cholinergic neurons are either inhibited or not affected by ACh/muscarine (Wu et al., 2000). Theoretically therefore, if a muscarinic tone was present on cholinergic neurons, then atropine should disinhibit these neurons, that is, increase their basal firing rate. Consistent with our recent findings, cholinergic neurons, as identified by Cy3–192IgG labeling,
were inhibited or not affected by ACh/muscarine (Wu et al., 2000). Of the 14 Cy3-labeled neurons inhibited by ACh/muscarine, 8 fired spontaneously at a rate of 2.7 \pm 0.4 Hz; muscarine reduced their rate to 0.6 \pm 0.3 Hz. The remaining 6 neurons were quiescent and showed a 1.4 \pm 0.24 mV hyperpolarization in response to ACh/muscarine. Interestingly only 1 of 14 Cy3-labeled neurons responded to atr/scop with a small increase in firing rate (data not shown). Thus, contrary to current thinking, intraseptal atropine would not decrease hippocampal ACh release. It may, however, increase hippocampal ACh release (Fig. 3).

In contrast to the Cy3–192IgG-labeled neurons mentioned above, Cy3–192IgG-unlabeled neurons, which are predominantly GABAergic (local or projection) and respond to ACh/muscarine with an excitation (Wu et al., 2000), were strongly inhibited by atr/scop (Fig. 3).

Noncholinergic MSDB neurons that are inhibited by atr/scop project to the hippocampus

Because a subpopulation of GABAergic neurons in the MSDB projects to the hippocampus (Wu et al., 2000), we hypothesized that the neurons that are inhibited by atr/scop might also project to the hippocampus. To test this hypothesis, we studied the effects of atr/scop on septohippocampal GABA neurons that were retro-
gradely labeled with rhodamine beads. If a rhodamine-labeled neuron responded to ACh/muscarine with an excitation, then it was assumed to be a septohippocampal GABAergic neuron because septohippocampal cholinergic neurons are not excited by muscarine (Wu et al., 2000). Atr/scop decreased basal firing by 73.6 ± 19% in 39% of septohippocampal GABA-type neurons identified by these criteria (n = 8; Fig. 4E). Whole-cell recordings further confirmed the neurons to be septohippocampal GABA-type on the basis of electrophysiological criteria (Fig. 4D) (Morris et al., 1999). The remaining neurons were not affected by atr/scop. Thus, a muscarinic tone is present on septohippocampal GABA neurons in vitro.

An M₃ receptor antagonist mimics the inhibitory effects of atr/scop on septohippocampal neurons

Because of the critical importance of the muscarinic tone in the MSDB in cognitive functioning, we next determined the specific receptor subtype(s) that might be involved in mediating the effects of endogenous ACh on septohippocampal GABA-type neurons. In a previous study we had found that the excitatory effects of exogenously applied muscarinic agonists in septohippocampal neurons are mediated primarily via the non-M₁ subtype of receptors. Involvement of the M₃ and possibly the M₅ subtype of muscarinic
receptors was indicated (Liu et al., 1998). These findings were strongly supported by the absence of M3 receptor immunoreactivity as well as mRNA (Buckley et al., 1988; Vilaro et al., 1994) and an abundance of M3 mRNA (Vilaro et al., 1994) and immunoreactivity (Levey et al., 1994; Rouse and Levey, 1996) in septohippocampal neurons. Low levels of M4 mRNA are also present in the MSDB (Vilaro et al., 1990).

We, therefore, tested the effects of 4-DAMP mustard (an M4-selective antagonist) as well as of pirenzepine and telenzepine (M1-selective receptor antagonists) on basal firing rates of MSDB neurons, some of which were confirmed to be septohippocampal by the use of either the technique of retrograde marking or the technique of antidromic activation (Fig. 4A,B) in sagittal slices. The role of M3 receptors in mediating the muscarinic tone in MSDB neurons could not be studied because an M3-selective antagonist is not yet available. As expected on the basis of our previous study (Wu et al., 2000), low nanomolar concentrations of 4-DAMP mustard, an irreversible antagonist that selectively inactivates M3 receptors but has no effect on M1, M2, M4, and M5 receptors (see Liu et al., 1998), reduced basal firing rates in 55% of the neurons tested (6 of 11). Of the 6 neurons that were inhibited by 4-DAMP mustard, 3 were confirmed to be septohippocampal neurons (Fig. 4F,H), a percentage similar to that observed with atr/scop (Fig. 4H). The change in basal firing rates was statistically significant (control rate, 3.2 ± 1 Hz; after M3 antagonist, 0.6 ± 0.5 Hz; Fig. 4F,H). The M4 receptor-selective antagonists pirenzepine and telenzepine also reduced basal firing rates in 19% of cells tested (3 of 16); 2 of 3 neurons were confirmed to be septohippocampal neurons. However, the reduction in basal firing rate was statistically insignificant (control rate, 2.8 ± 1.3 Hz; after M1 antagonist, 0.1 ± 0.05 Hz; Fig. 4G,H). Thus, M3 receptors contribute to the muscarinic tone in the MSDB, suggesting that M3 receptor agonists could be beneficial in treating cognitive deficits that are associated with a loss of muscarinic tone in the MSDB.

**DISCUSSION**

In the present study we have demonstrated two key features about the muscarinic tone in the MSDB. First, the muscarinic tone in the MSDB is caused by a tonic release of ACh that occurs from within the MSDB, presumably via axon collaterals of spontaneously firing septohippocampal cholinergic neurons. Second, the locally released ACh in the MSDB provides a profound excitatory drive to the septohippocampal GABA neurons but has little or an opposing effect on the septohippocampal cholinergic neurons. Thus, the memory-impairing effects of muscarinic receptor antagonists cannot be attributed to a decrease in hippocampal ACh release. Instead, a decrease in septohippocampal GABA release may underlie the effects of muscarinic receptor antagonists on cognitive functions.

**A muscarinic tone is intrinsic to the MSDB**

Behavioral studies have long documented the presence of a muscarinic tone in the brain of various species; a blockade of this tone produces amnesia. As mentioned in the introductory remarks, experimental studies indicate that the MSDB may be a key locus for the mnemonic effects of muscarinic antagonists. The present study using electrophysiological recording techniques in rat brain slices not only confirms the presence of such a tone in single MSDB neurons but provides evidence that the muscarinic tone is produced from within the MSDB. This tone presumably originates from the septohippocampal cholinergic neurons present within the MSDB, which have anatomically been demonstrated to send collaterals to neurons within the MSDB (Brauer et al., 1998). By the use of two different techniques of identification, 55% of cholinergic neurons in our brain slice preparations were found to be spontaneously firing and therefore capable of releasing ACh locally in an impulse-dependent manner. Accordingly, a blockade of synaptic transmission, using low-Ca²⁺, high-Mg²⁺ external solutions, was also found to mimic the effects of muscarinic receptor antagonists and inhibit a subpopulation of MSDB neurons. The presence of spontaneously firing cholinergic neurons within the MSDB that are capable of releasing acetylcholine under basal conditions is consistent with microdialysis data obtained both in vivo and in vitro, in which impulse-dependent ACh release has been recorded both locally within the septum and in the hippocampus (Moor et al., 1995).

Because the present study was performed in younger rats, it is possible that the muscarinic tone demonstrated in this study may be of a different magnitude in animals of different ages, possibly because of factors such as the pruning of axon collaterals or a loss of cholinergic neurons with age. In this regard, it should be mentioned that microdialysis studies have detected higher ACh release in septal slices taken from 2.5- to 3-month-old rats compared with those of 2-week-old rats (Disko et al., 1999). Whether basal ACh release is reduced in the septum of aged rats (22–24 week rats) is not known. However, because hippocampal ACh release is clearly reduced in aged rats (Vannucchi et al., 1997), septal ACh release is likely to be reduced too. Additionally, because behavioral deficits in mnemonic functions that occur in aged animals can be reversed by intraseptal applications of muscarinic agonists (Markowska et al., 1995), the intraseptal muscarinic tone is likely to be reduced in aged animals.

It is conceivable that ACh released via the extrinsic brainstem afferents may also contribute to the muscarinic tone in the MSDB in vivo both in young and aged rats. If so, then muscarinic receptor antagonists would produce an even greater decrease in septohippocampal GABA transmission. Septohippocampal cholinergic transmission, on the other hand, could get enhanced as cholinergic neurons are inhibited by muscarine (Wu et al., 2000).

**The muscarinic tone in the MSDB provides an excitatory drive to the septohippocampal GABA but not to the septohippocampal cholinergic neurons**

A second major finding of this study is that the muscarinic tone in the MSDB provides a profound excitatory drive to the noncholinergic septohippocampal GABAergic-type neurons but has little or an opposing effect on the septohippocampal cholinergic neurons. Thus, only 1 of 14 cholinergic neurons identified by the use of the selective fluorescent marker Cy3–192IgG responded to atr/scop with an increase in firing rate, whereas 47% of Cy3–192IgG-unlabeled neurons (which are primarily GABAergic), some of which were confirmed to be septohippocampal, were strongly inhibited by atr/scop. These findings are consistent with the presence of ChAT–immunoreactive terminals contacting nonimmunoreactive perikarya in the MSDB that suggests a cholinergic innervation of noncholinergic MSDB neurons (Bialowas and Frotscher, 1987) and with the more recent demonstration of local cholinergic boutons contacting parvalbumin-containing septohippocampal GABAergic neurons (Brauer et al., 1998).

Thus, contrary to current thinking, intraseptal atropine would not decrease hippocampal ACh release. It may, however, increase hippocampal ACh release. These findings are consistent with the reported increase in hippocampal ACh release after intraseptal atropine in microdialysis studies (Moor et al., 1995). Thus, the amnesic effects of intraseptal atr/scop and possibly systemic atr/scop cannot be attributed to a decrease in ACh release in the hippocampus. Instead, a decrease in septohippocampal GABA release, via a disinhibitory mechanism (see below), may mediate the amnesic effects of muscarinic receptor antagonists.

Similar to muscarinic receptor antagonists, opioids, acting via µ receptors, also inhibit a subpopulation of septohippocampal GABA neurons, and interestingly intraseptal infusions of opioids impair performance in learning and memory tasks (see Alreja et al., 2000).

**M₃ receptors contribute to the effects of muscarinic receptor antagonists in the MSDB**

Another important finding of this study is that locally released ACh maintains impulse flow in the septohippocampal GABA pathway in part via M₃ muscarinic receptors. Thus, an M₃ receptor antagonist was found to mimic the effects of atr/scop in a subpopulation of
MSDB neurons in brain slices. This conclusion is consistent with the presence of M2 receptor message in SHNs (Levey et al., 1994; Vilaro et al., 1994; Rouse and Levey, 1996) and with our previous finding in which effects of exogenous ACh/muscarine in septohippocampal GABA-type neurons were also blocked by an M2-selective antagonist (Liu et al., 1998). The relatively weaker effects observed with M1 antagonists in this study are also consistent with the rather low levels of M1 receptor message in MSDB neurons (Buckley et al., 1988; Vilaro et al., 1994). Involvement of M2 or other as yet undiscovered muscarinic receptors is also likely but cannot be tested at the present time because of lack of adequate tools. Because of the reported involvement of M1 receptors in mediating muscarinic responses in the hippocampus, the last decade witnessed the development of various M1-selective agonists. Our results suggest that M1-selective antagonists may be even more beneficial for improvement of cognitive deficits. As such it would be interesting to determine whether a functional loss of M1 receptors would mimic the amnesic effects of atropine/scopolamine in behavioral studies.

Implications of the findings

A muscarinic receptor antagonist-induced decrease in septohippocampal GABA release could, theoretically, disinhibit large numbers of hippocampal GABAergic neurons and increase both the feedback and feedforward type of local hippocampal inhibition of pyramidal cells (Freund and Antal, 1988; Toth et al., 1997) because the muscarinic tone in the MSDB originares from within the MSDB, a loss of septohippocampal cholinergic neurons, as occurs in normal aging, Alzheimer's disease, Parkinson's disease, Lewy body dementia, Down syndrome, and Korsakoff's disease, would not only decrease the direct excitatory effects of ACh in the hippocampus (by decreasing ACh release) but would also reduce the muscarinic tone within the MSDB and therefore severely disable both the cholinergic and GABAergic limbs of the septohippocampal pathway. Restoration of cholinergic function both in the hippocampus and the septum may, therefore, be critical for successful treatment of cognitive deficits associated with various neurodegenerative disorders. An M1 receptor agonist may prove useful in this regard provided the septohippocampal GABA neurons are still functional. It may therefore be worthwhile to determine the status of the parvalbumin-containing septohippocampal GABAergic neurons in postmortem brains derived from patients with such neurodegenerative disorders.

REFERENCES

Kopelman MD, Corn TH (1988) Cholinergic ‘blockade’ as a model for cholinergic depletion. A comparison of the memory deficits with those of muscarinic drugs. Thus, an improvement or impairment in performance of septohippocampal-related learning and memory tasks can occur without an accompanying increase or decrease, respectively, in hippocampal ACh release. The reported findings thus suggest a fundamental revision in our understanding of the septohippocampal mechanisms that may underlie learning and memory functions.
Additionally, because the muscarinic tone in the MSDB originates from within the MSDB, a loss of septohippocampal cholinergic neurons, as occurs in normal aging, Alzheimer’s disease, Parkinson’s disease, Lewy body dementia, Down syndrome, and Korsakoff’s disease, would not only decrease the direct excitatory effects of ACh in the hippocampus (by decreasing ACh release) but would also reduce the muscarinic tone within the MSDB and therefore severely disable both the cholinergic and GABAergic limbs of the septohippocampal pathway. Restoration of cholinergic function both in the hippocampus and the septum may, therefore, be critical for successful treatment of cognitive deficits associated with various neurodegenerative disorders. An M1 receptor agonist may prove useful in this regard provided the septohippocampal GABA neurons are still functional. It may therefore be worthwhile to determine the status of the parvalbumin-containing septohippocampal GABAergic neurons in postmortem brains derived from patients with such neurodegenerative disorders.

Figure 5. Schematic figure shows that ACh released via axon collaterals of septohippocampal cholinergic neurons provides an excitatory drive to the septohippocampal GABA neurons partly via M1 receptors. The muscarinic receptor antagonists atropine or scopolamine block this muscarinic tone and reduce impulse flow in the disinhibitory septohippocampal GABA pathway. + +, excitation.


