Ipidacrine (NIK-247): A Review of Multiple Mechanisms as an Antidementia Agent

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INTRODUCTION

Ipidacrine (NIK-247, 9-amino-2,3,5,6,7,8-hexahydro-1H-cyclopenta[b]quinoline monohydrochloride monohydrate) is a novel substance synthesized by the National Research Center for Biologically Active Compounds in the Russian Federation. Ipidacrine was earlier referred to by the chemical name amiridine (7). This compound contains the structure of 4-aminopyridine and is structurally very similar to tacrine (9-amino-1,2,3,4-tetrahydroacridine hydrochloride hydrate), as is shown in Fig. 1. It has been reported that ipidacrine blocks specific [3H]tacrine binding (43). Tacrine is an antidementia agent that can inhibit acetylcholinesterase (EC 3.1.1.7, AChE) (21,26,48,50). Senile dementia has been associated with a loss of cholinergic neurotransmission, which is essential for some cognitive functions (20,53). Degeneration of basal forebrain cholinergic neurons in the nucleus basalis of Meynert (NBM) and deficiencies of acetylcholine and choline acetyltransferase (EC 2.3.1.6.) are known to occur in Alzheimer’s disease (10,72). This cholinergic hypothesis has led to the development of compounds that are capable of improving cholinergic neurotransmission in the brain. Among the various approaches to enhancement of the cholinergic system, inhibition of the degrading enzyme (AChE) is presently the most promising in terms of providing candidate drugs for treatment of patients with dementia (16,32,57,63). Recently, tacrine and E-2020 (1-benzyl-4-[{5,6-dimethoxy-1-indanon}-2-yl]methylpiperidine hydrochloride, Eisai Co., Ltd., Tokyo, Japan), a pure AChE inhibitor, won FDA approval for treating Alzheimer’s Disease (Fig. 1) (57). A number of additional AChE inhibitors await approval; however, CI-1002 is not one of them, since it was disqualified in phase I clinical trials. Therefore, we discuss in this paper
the effects of ipidacrine in comparison with those of tacrine and E-2020 on various models of amnesia.

Pharmacological experiments with ipidacrine have been carried out by many groups, demonstrating that ipidacrine is a useful drug for improving various types of amnesia in rodents (33,47,49,67,70,74,76,77). Recently, we have reported that the potency of ipidacrine in improving scopolamine-induced impairment of passive avoidance is nearly the same as that of tacrine (33). However, the in vitro potency of ipidacrine for inhibiting AChE was about one-third that of tacrine (33). Therefore, the potency of ipidacrine in improving scopolamine-induced amnesia cannot be explained only via the mechanism of AChE inhibition.

In this review, we focus on the mechanisms of ipidacrine as an antidementia agent for improving various types of amnesia models, mainly from the viewpoint of the central cholinergic system, in behavioral pharmacology, biochemistry, electrophysiology, and pharmacokinetics.
CHEMISTRY

Four different chemical categories of AChE inhibitors are in current use or clinical trials. These include aminopyridines (e.g., tacrine), organophosphates (e.g., metrifonate), carbamates (e.g., pyridostigmine), and others, such as huperzine. Ipidacrine is an aminopyridine and is structurally similar to tacrine, as shown in Fig. 1.

Ipidacrine is a white to off-white solid; the molecular weight is 242.75 pKₐ. The compound is very soluble in formic acid, freely soluble in distilled water and methanol, soluble in ethanol, slightly soluble in chloroform, and insoluble in ethyl ether. Ipidacrine is hydrophobic, having a log P value of 0.03 at pH 8.0. The pKₐ of ipidacrine is 10.3, indicating that the molecule is almost fully protonated at physiological pH (59).

BEHAVIORAL PHARMACOLOGY

Improvement of Dysfunction in Learning and Memory

The principal clinical feature of Alzheimer’s disease is impairment of cognitive function. Since scopolamine, a muscarinic antagonist, impairs learning and memory in rats (15,33,74,77) and humans (13,64), the scopolamine-induced amnesia model has been used extensively in the search for cognitive enhancers, ipidacrine is effective in various amnesia models which involve impairment of working and reference memory, as summarized in Table 1. In brief, Nabeshima et al. (47) reported that a single administration of ipidacrine improved the impairment of the passive avoidance response induced by various treatments such as cycloheximide, picrotoxin, phencyclidine, and electroconvulsive shock. These results were confirmed by other researchers with respect to working memory impairment (amnesia induced by scopolamine, hippocampal lesions, or cerebral ischemia) using the three-panel runway task (74); to reference memory impairment (amnesia induced by scopolamine and nucleus basalis magnocellularis [NBM] lesions) using the passive avoidance task in rats (33,67,77); and water maze task (49). Thus, these data are in line with the idea that the spectrum of the antiamnesic effects of ipidacrine is multifarious.

We found that the effects of ipidacrine in scopolamine-induced amnesia were equal to those of tacrine and E-2020 (33). Moreover, it has been reported that ipidacrine is 30 times more potent than tacrine and three times more potent than E-2020 in scopolamine-induced amnesia or the passive avoidance task in rats (70). These results show that ipidacrine has identical or more potent antiamnesic effects than tacrine or E-2020 in vivo.

On the other hand, less attention has been paid to obtaining information on the effects of repeated administration of ipidacrine relative to the impairment of learning and memory. Notably, the effectiveness of repeated administration of ipidacrine (for 5 d), at 1 mg/kg p.o., was much greater than that of a single administration in the Morris water maze task (49). It has also been reported that the repeated administration of ipidacrine or tacrine (either at 1 or 3 mg/kg p.o., for 3 w) improved amnesia induced by NBM lesions in the passive avoidance task in rats (67). These data suggest that by repeated adminis-
**TABLE 1. Summary of anti-dementia effects and side effects of ipidacrine**

<table>
<thead>
<tr>
<th>Action</th>
<th>Task</th>
<th>Model</th>
<th>Species</th>
<th>Dose, p.o.</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-amnesia (passive avoidance)</td>
<td>Reference memory</td>
<td>Cycloheximide (30 mg/kg s.c.)</td>
<td>mouse</td>
<td>0.03, <strong>0.1</strong>, <strong>0.3</strong>, 1, 3, 10</td>
<td>(46)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Electroconvulsion</td>
<td></td>
<td>0.03, <strong>0.1</strong>, <strong>0.3</strong>, 1, 3, 10</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phencyclidine (30 mg/kg s.c.)</td>
<td></td>
<td>0.03, <strong>0.1</strong>, <strong>0.3</strong>, 1, 3, 10</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Picrotoxin (3 mg/kg s.c.)</td>
<td></td>
<td>0.03, 0.1, <strong>0.3</strong>, 1, 3, 10</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CO</td>
<td></td>
<td>0.01, <strong>0.03</strong>, <strong>0.1</strong>, <strong>0.3</strong>, 1, 3, 10</td>
<td>(75)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Scopolamine (0.5 mg/kg s.c.)</td>
<td>rat</td>
<td><strong>0.13</strong>, <strong>0.39</strong>, 1.3, 3.9, 13</td>
<td>(69)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>0.1</strong>, <strong>0.3</strong>, 1</td>
<td>(33)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1, 3</td>
<td>(66)</td>
</tr>
<tr>
<td>(Water maze)</td>
<td></td>
<td></td>
<td></td>
<td>0.1, <strong>0.3</strong>, 1</td>
<td>(48)</td>
</tr>
<tr>
<td>Work memory</td>
<td></td>
<td></td>
<td></td>
<td>3.2, <strong>10</strong>, <strong>18</strong></td>
<td>(73)</td>
</tr>
<tr>
<td>(3-panel runway)</td>
<td></td>
<td></td>
<td></td>
<td>10, 32</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>3.2</strong>, <strong>10</strong></td>
<td></td>
</tr>
<tr>
<td>Side effects</td>
<td>Hypersalivation</td>
<td></td>
<td>mouse</td>
<td>34</td>
<td>(69)</td>
</tr>
<tr>
<td></td>
<td>Hypothermia</td>
<td></td>
<td></td>
<td>52</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypolocomotion</td>
<td></td>
<td>rat</td>
<td>1, 3, <strong>10</strong></td>
<td>(33)</td>
</tr>
<tr>
<td></td>
<td>Miosis</td>
<td></td>
<td></td>
<td>0.3, 1, <strong>3</strong>, <strong>10</strong>, <strong>30</strong></td>
<td>(76)</td>
</tr>
<tr>
<td></td>
<td>Hypersalivation</td>
<td></td>
<td></td>
<td>0.3, 1, <strong>3</strong>, <strong>10</strong>, <strong>30</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypothermia</td>
<td></td>
<td></td>
<td>0.3, 1, <strong>3</strong>, <strong>10</strong>, <strong>30</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tremor</td>
<td></td>
<td></td>
<td>0.3, 1, <strong>3</strong>, <strong>10</strong>, <strong>30</strong></td>
<td></td>
</tr>
</tbody>
</table>

Bold letters indicate effective dose.
Ipidacrine is more potent as antiamnesic than by single administration, and it is difficult to induce tolerance with this agent.

**Spontaneous Movement and Other Effects**

Ipidacrine significantly decreased spontaneous movements at 10 mg/kg p.o., but not at 1 or 3 mg/kg p.o. At 10 mg/kg p.o. either tacrine or E-2020 also decreased spontaneous movements.

It is well recognized that cholinomimetic drugs cause side effects such as nausea, abdominal cramps, Parkinson-like syndrome, depression, tremor and hypersalivation (6,8,11,52,55,62,66,71). Ipidacrine, at a single oral dose of 3 mg/kg, decreased pupil size and increased salivation. At 30 mg/kg p.o., it decreased body temperature and induced tremor (77). A single oral dose of tacrine produced miosis (0.3 mg/kg), hypersalivation (1 mg/kg), hypothermia (10 mg/kg), and tremor (10 mg/kg). The antiamnesic doses of ipidacrine, tacrine, and E-2020 were, respectively, about 1/130, 1/2.3, and 1/11 of doses that caused central side effects such as hypothermia (70). These results show that ipidacrine is more selective as an antiamnesic than either tacrine or E-2020.

**BIOCHEMICAL STUDIES**

*In Vitro Inhibition of AChE and BuChE Activity*

Acetylcholine is distributed throughout the central nervous system, with high concentrations in the cerebral cortex, thalamus, and various nuclei in the basal forebrain (39,44). Acetylcholine is hydrolyzed by cholinesterase. The inhibition of the degrading enzyme AChE is presently the most promising in terms of providing candidate drugs for treatment of patients with dementia. However, there are two cholinesterase enzymes: AChE and butyrylcholinesterase (BuChE) (EC 3.1.1.8). Although their molecular forms are similar, the two enzymes are distinct entities, and are encoded for by different genes (9). The localization of AChE was studied by electron microscopic and histochemical techniques; the activity was found at membranes of all kinds both in the central and peripheral nervous systems (69). In the blood, erythrocytes contain only AChE while plasma contains BuChE (9).

Ipidacrine, tacrine, and E-2020 showed a concentration-dependent inhibition of AChE activity, when measured by the Ellman colorimetric cholinesterase assay (14). The pattern of AChE inhibition by ipidacrine and tacrine was reversible, determined by dilution assay (26,33). The IC$_{50}$ values of ipidacrine, tacrine, and E-2020 for the inhibition of human red blood cell AChE are shown in Table 2. In addition, tacrine inhibited BuChE more strongly than AChE. The potencies of ipidacrine in inhibiting both AChE and BuChE were one-third that of tacrine. E-2020 had a poor effect on BuChE. The potencies of ipidacrine in inhibiting AChE and BuChE were 1/13 and 100 times that of E-2020, respectively (33).
Ex Vivo Inhibition of Brain AChE by Ipidacrine

Ipidacrine at 10 mg/kg p.o. significantly inhibited AChE activity in rat cerebral cortex 0.5, 1, and 3 h after oral administration of ipidacrine (27). Compared with in vitro tests, it is very difficult to exactly assess the inhibitory effects of reversible AChE inhibitors on brain AChE activity ex vivo, since the inhibitory effects reverse rapidly when preparing the tissue for assay (21, 60, 68). Nevertheless, it has been reported that tacrine and E-2020 inhibit AChE activity at 10 and 3 mg/kg p.o., respectively, in the brain (75). These results show that the inhibitory effect of ipidacrine in ex vivo tests is about one-third to equal to that of tacrine or E-2020 on brain AChE, respectively.

Ipidacrine (5 and 10 mg/kg p.o.) and tacrine (5 mg/kg p.o.) increased extracellular acetylcholine concentration in the cerebral cortex, as measured by microdialysis technique (27). The degree of increase induced by ipidacrine at 10 mg/kg was almost equal to that induced by tacrine at 5 mg/kg (27). Also, tacrine (5 mg/kg i.p.) and E-2020 (0.65 and 2 mg/kg i.p.) increased the concentration of acetylcholine in the hippocampus (as measured by microdialysis technique) (28). Moreover, ipidacrine and tacrine at 1 and 3 mg/kg p.o. increased acetylcholine content in the frontal cortex in NBM-lesioned rats (67).

Interactions with Muscarinic Receptors

Tacrine binds to muscarinic receptors, which would oppose the beneficial effects resulting from AChE inhibition (29, 30). Accordingly, we investigated the effects of ipidacrine on muscarinic receptor subtypes and compared them with those of tacrine in rats. At least three pharmacologically distinct muscarinic receptor subtypes have been defined: M1 receptors, which are located mainly in nervous tissues; M2 receptors, which are located in nervous and cardiac tissues; and M3 receptors, which are located in nervous and glandular tissues (25). At least five different molecular subtypes, m1 to m5, have been defined. The molecular subtypes m1, m2, and m3 represent the pharmacological subtypes M1, M2, and M3, respectively (22). Binding studies indicate that in Alzheimer’s disease M1 receptors are retained at near-normal levels (1, 19, 41), whereas M2 receptors are reduced (1, 41) or increased (23) in number.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>AChE IC50 (M)</th>
<th>BuChE IC50 (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipidacrine</td>
<td>1.0 × 10^-6</td>
<td>1.9 × 10^-7</td>
</tr>
<tr>
<td>Tacrine</td>
<td>2.9 × 10^-7</td>
<td>6.2 × 10^-8</td>
</tr>
<tr>
<td>E-2020</td>
<td>3.7 × 10^-8</td>
<td>1.5 × 10^-5</td>
</tr>
</tbody>
</table>

Abbreviations: AChE, acetylcholinesterase; BuChE, butyrylcholinesterase; RBC, red blood cell.
Ipidacrine, tacrine, and E-2020 inhibited the binding of \([^{3}H]\)pirenzepine (M₁), \([^{3}H]\)AF-DX 384 (M₂), and \([^{3}H]\)4-DAMP (M₃) in a dose-dependent manner (34). The IC₅₀ values for ipidacrine, tacrine, and E-2020 are shown in Table 3. Gpp[NH]p, a GTP analogue slightly shifted to the right the curve of displacement of \([^{3}H]\)AF-DX 384 binding, but not those of displacement of \([^{3}H]\)pirenzepine and \([^{3}H]\)4-DAMP binding, by ipidacrine (34). In addition, ipidacrine moderately decreased the heart rate in right atrial preparations (predominantly M₂ receptors), but did not decrease it to below 50% of the control level. Thus, ipidacrine acts as an M₁ antagonist, M₂ partial agonist, and M₃ antagonist.

Kiefer-Day and colleagues suggested that individual inter-patient variability and inconsistent results in clinical studies obtained with tacrine may be related to the blockade of muscarinic receptors, which would oppose the beneficial effects resulting from AChE inhibition (29,30). There is no significant difference in the potency of the muscarinic antagonistic effects and AChE inhibitory effects of tacrine (29,30,33). However, since the slope factor of tacrine is steeper for M₁ receptors than it is for inhibiting AChE activity (slope factor = 1.74), at higher concentrations the inhibition by tacrine of ligand binding to M₁ receptors is equal to its inhibition of AChE activity. These findings suggest that at relatively high doses of tacrine the cholinergic effects of tacrine are reduced by its antagonistic effects. On the other hand, although ipidacrine acts as an M₁ antagonist, M₂ partial agonist, and M₃ antagonist, its potency at the muscarinic receptors is lower than its AChE inhibitory potency.

**ELECTROPHYSIOLOGICAL PHARMACOLOGY**

**Spontaneous EEG**

Centrally acting cholinomimetics produce arousal patterns (decreasing total power and delta wave activity) on the cortical EEG (17,24). The EEG recorded from patients with Alzheimer’s disease can be characterized by alpha slowing and generalized predominance of delta and theta activities (54). Furthermore, animal lesions of the NBM reduce power in the beta-frequency band. Thus, the generalized EEG slowing observed in Alzheimer’s disease may reflect, at least in part, a cortical hypocholinergic state associated with basal forebrain degeneration.

**TABLE 3.** Effects of ipidacrine, tacrine, E-2020, and atropine on muscarinic receptor subtypes

<table>
<thead>
<tr>
<th>Drugs</th>
<th>M₁ IC₅₀ (M)</th>
<th>slope factor</th>
<th>M₂ IC₅₀ (M)</th>
<th>slope factor</th>
<th>M₃ IC₅₀ (M)</th>
<th>slope factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipidacrine</td>
<td>4.4 × 10⁻⁶</td>
<td>1.09</td>
<td>1.1 × 10⁻⁵</td>
<td>1.27</td>
<td>1.5 × 10⁻⁵</td>
<td>1.02</td>
</tr>
<tr>
<td>Tacrine</td>
<td>5.8 × 10⁻⁷</td>
<td>1.74</td>
<td>2.0 × 10⁻⁶</td>
<td>1.32</td>
<td>5.8 × 10⁻⁶</td>
<td>1.47</td>
</tr>
<tr>
<td>E-2020</td>
<td>4.5 × 10⁻⁷</td>
<td>0.93</td>
<td>1.2 × 10⁻⁶</td>
<td>1.32</td>
<td>4.2 × 10⁻⁶</td>
<td>1.01</td>
</tr>
<tr>
<td>Atropine</td>
<td>1.5 × 10⁻⁹</td>
<td>1.78</td>
<td>7.7 × 10⁻¹⁰</td>
<td>1.29</td>
<td>8.2 × 10⁻¹⁰</td>
<td>1.16</td>
</tr>
</tbody>
</table>
In normal rats, ipidacrine at 1 and 3 mg/kg p.o. did not show any effects on the EEG, but at 10 mg/kg p.o. it significantly lowered the total power of cortical EEG (37). Tacrine, at 3 and 10 mg/kg p.o., also decreased the total power of cortical EEG in normal rats. In NBM-lesioned rats, decreases of delta-wave activity as well as of total power of the cortical EEG were observed with both ipidacrine and tacrine at 3 mg/kg p.o. (37). Thus, ipidacrine also showed effectiveness against hypofunction of the cholinergic system, as viewed from changes in cortical EEG in rats.

Long-Term Potentiation

Long-term potentiation (LTP) in the hippocampus is a widely used model system for the study of mechanisms of synaptic plasticity that are believed to be involved in certain types of learning and memory (3,4). In the major excitatory pathways within the hippocampus, repeated stimulation can induce an immediate and prolonged increase in the efficiency of synaptic transmission. LTP is known to play a role in learning and memory in rats (2,12,45). Much research has recently focused on modulation of the amplitude of population spikes and LTP by the central cholinergic system in rat hippocampal slices, since a triangular relationship exists between LTP, the brain cholinergic system, and learning and memory function, as described previously (5,73).

Population spikes evoked by electrical stimulation of the stratum radiatum were recorded in the pyramidal cell layer of the CA1 region of the isolated hippocampus. According to Bliss and Collingridge (3) LTP is an increase in the population spike amplitude, lasting for > 1 h. In addition, the drug-induced increase in the population spike amplitude
is significantly different from the population spike amplitude before drug application (58). Ipidacrine at $1 \times 10^{-7}$ to $1 \times 10^{-5}$ M increased the amplitude of these spikes in a dose-dependent manner (Fig. 2) (35). The increase of population spikes by ipidacrine outlasted, for 2 h, its presence. In addition, the increase of population spikes recovered to normal after washout of ipidacrine. Therefore, it was concluded that ipidacrine induced LTP by itself. On the other hand, tacrine and physostigmine, at $1 \times 10^{-7}$ to $1 \times 10^{-5}$ M, did not increase the amplitude of population spikes, and did not induce LTP by themselves (Fig. 2). The increase in the amplitude of population spikes induced by ipidacrine was completely blocked by atropine ($IC_{50} = 4.3 \times 10^{-8}$ M) and by pirenzepine ($IC_{50} = 9.1 \times 10^{-7}$ M). Carbachol (non-selective muscarinic agonist), at $3 \times 10^{-6}$ M, also increased the amplitude of population spikes in the presence of $3 \times 10^{-7}$ pirenzepine ($M_{1}$ muscarinic antagonist). Thus, the $M_{2}$ muscarinic agonistic action of carbachol may increase the amplitude of population spikes. These findings indicate that the LTP induced by ipidacrine is due to its $M_{2}$ muscarinic agonistic effect in the CA1 region of the rat hippocampus. It is expected that LTP potentiation by ipidacrine may be useful in the treatment of patients with Alzheimer’s disease.

### Blockade of $K^{+}$ and $Na^{+}$ channels

Ipidacrine contains the structure of 4-aminopyridine, which is a $K^{+}$-channel blocker. Effects of $K^{+}$-channel blockers have been explained as the result of prolongation of impulses at the presynaptic terminal, which would increase transmitter release and facilitate synaptic transmission of substances such as acetylcholine, norepinephrine, dopamine, and glutamate (38,40). The effect of ipidacrine on ionic currents was examined in an artificial node of the crayfish giant axon under voltage clamp. When applied externally, ipidacrine reversibly suppressed both inward and outward currents. Ipidacrine and tacrine blocked $K^{+}$ channels in a concentration-dependent manner. The $IC_{50}$ values of ipidacrine and tacrine for the blocking of $K^{+}$ channels were $1.0 \times 10^{-3}$ M and $5.0 \times 10^{-4}$ M, respectively (36). However, in its blocking action ipidacrine was less potent than 4-aminopyridine. In addition, ipidacrine and tacrine blocked $Na^{+}$ channels in a concentration-dependent manner. The $IC_{50}$ value of ipidacrine for blocking $Na^{+}$ channels was $4 \times 10^{-4}$ M (36). Therefore, the blocking effects of ipidacrine on $K^{+}$ and $Na^{+}$ channels are not clinically important, since the $IC_{50}$ value of ipidacrine for blocking channels is about 1000 times higher than that for inhibiting AChE.

### PHARMACOKINETICS

In patients with Alzheimer’s disease, the cholinergic deficits in the neocortex and hippocampus have been reported to correlate with the cognitive impairment (20,51,53). Interestingly, in our pharmacokinetics study, higher drug levels were observed mainly in the cortex and hippocampus (49). The previously found passive avoidance response may have involved the cortical cholinergic system (33), since this task involves a form of reference memory known to depend on an intact frontal cortex (56) and is impaired by cholinergic
antagonists such as atropine and scopolamine (18,33,61). The previously described water maze task may involve a form of reference memory and is exquisitely sensitive to hippocampal lesions, since spatial learning is a primary function of the rodent hippocampus (46,49,65).

Thus, the higher drug levels of ipidacrine were observed mainly in the cortex and the hippocampus, where both play important roles in learning and memory. Moreover, ipidacrine was rapidly taken up into the brain (within 5 min). The highest peak for the drug level of ipidacrine at 1 mg/kg p.o. was 32.9 ng/g in rats (49). For inhibiting AChE activity, the IC_{50} value of ipidacrine was 1 \times 10^{-6} M (33). Taken together, the drug level seemed not to be enough to reach the IC_{50} value for inhibiting AChE even at the highest peak (1.4 \times 10^{-7} M) after a single oral administration of ipidacrine at 1 mg/kg in rats. The drug level of brain ipidacrine was almost equal to its serum level, whereas the drug level of brain tacrine was shown to be 10 to 30 times higher than the blood level (42,48). Kiefer-Day and Fakahany have reported that the drug levels of tacrine in brain were sufficient to inhibit 78 to 80% of brain AChE activity following 3 mg/kg tacrine (31). Further, the brain levels of E-2020 were six to eight times higher than those of plasma at 3 and 10 mg/kg after oral administration (75). It is unlikely, therefore, that ipidacrine enters the brain better than either tacrine or E-2020.

**SUMMARY AND CONCLUSION**

From these results, the potency of ipidacrine in improving scopolamine-induced amnesia cannot be explained only by inhibition of AChE, but also by brain penetration. Nevertheless, ipidacrine, tacrine, and E-2020 were essentially equipotent in improving scopolamine-induced amnesia (33,70,77). Accordingly, it is likely that the multiple ameliorating effects, i.e., inhibition of AChE (33), augmentation of LTP (35), and very weak antagonistic action at the central muscarinic receptors (34), may all contribute to the in vivo activity of ipidacrine as an antiamnesic agent. Finally, the pharmacological profile of ipidacrine shows that it is an orally active reversible AChE inhibitor and an LTP enhancer, suggesting that ipidacrine may be a useful drug for the treatment of patients with Alzheimer’s disease.

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