may be of therapeutic relevance. As 5HT is involved in the expression of a wide range of behaviours such as sleep, aggression and mood, it may be that a serotonergic therapy in Alzheimer's disease could ameliorate both the cognitive and non-cognitive symptoms of the disease.


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### Table 2. Effects of 8-OH-DPAT on delayed non-match-to-sample

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Delay(s)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline (n = 7)</td>
<td></td>
<td>88 ± 5</td>
<td>84 ± 3</td>
<td>79 ± 3</td>
<td>79 ± 4</td>
<td>60 ± 6</td>
<td>50 ± 6</td>
</tr>
<tr>
<td>8-OH-DMAT</td>
<td></td>
<td>95 ± 4</td>
<td>93 ± 2</td>
<td>91 ± 2</td>
<td>77 ± 8</td>
<td>56 ± 8</td>
<td>55 ± 4</td>
</tr>
<tr>
<td>100 µg/kg (n = 6)</td>
<td></td>
<td>95 ± 2</td>
<td>92 ± 4</td>
<td>83 ± 5</td>
<td>83 ± 5</td>
<td>57 ± 5</td>
<td>56 ± 3</td>
</tr>
<tr>
<td>200 µg/kg (n = 6)</td>
<td></td>
<td>95 ± 2</td>
<td>92 ± 4</td>
<td>83 ± 5</td>
<td>83 ± 5</td>
<td>57 ± 5</td>
<td>56 ± 3</td>
</tr>
</tbody>
</table>

Disinhibitory properties of β-carboline antagonists of benzodiazepine receptors: a possible therapeutic approach for senile dementia?

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The original idea suggesting that antagonists or inverse agonists at the benzo diazepine receptor may exert prom ne stic or nootropic properties, was based on a simple analogy: as benzodiazepine receptor agonists induce anterograde amnesia, antagonists or, at least, inverse agonists at the benzodiazepine receptor should produce effects opposite to those of agonists, even at the level of information processing. The basis of both amnestie and prom nestic properties of agonists and antagonists/inverse agonists, respectively, has been assumed to be essentially similar. Thus, the amnestie properties of agonists seem to be primarily the result of an impairment of stimulus filtering (Cole, 1986; Clark et al., 1983; Rohrs et al., 1983) which could be measured best in signal-detection tasks. Accordingly, the beneficial effects of inverse agonists in cognitive tasks have been assumed to depend primarily on improved learning in contrast to effects on retrieval of information. Subsequently, in dealing with the pharmacological profile of the β-carboline ZK 93 426, an antagonist at the benzodiazepine receptor, the hypothesis that such compounds produce prom nestic effects on the basis of a disinhibitory mechanism at cortical cholinergic afferent neurons has been developed (Sarter et al., 1988). The substantia innominata seems likely to represent one major anatomical locus of such a GABAergic–cholinergic interaction.

Effects of the agonist β-carboline ZK 93 426 at the GABA–benzodiazepine receptor complex

ZK 93 426 was demonstrated to be a potent inhibitor of [3H]flunitrazepam binding in vitro (IC50 = 0.4–0.7 nm) and of
\[ \text{Biodemizepine receptors} \] was enhanced in the presence of \[ \text{TBPS} \] (TBPS ratio) which is a characteristic value for partial inverse agonist properties (Jensen et al., 1984).

**General pharmacological profile of ZK 93 426**

Briefly, ZK 93 426 in most of the classical pharmacological tests lacked overt effects; it showed proconflict effects in the water-lick conflict test but also some weak anticonvulsant properties and it antagonized convulsions induced by the inverse agonist \( \beta \)-carboline, DMCM. Accordingly, ZK 93 426 seems to be an antagonist at the benzodiazepine receptor with some partial agonist and some partial inverse agonist features, depending on the particular test. Although the pharmacological profile of Ro 15-1788 overlaps widely with that of ZK 93 426, the latter possesses more agonist-like pharmacological properties (Jensen et al., 1984).

**Cognitive effects of ZK 93 426**

**Antagonism of different behavioural effects of scopolamine**

The anticholinergic scopolamine has been shown to impair predominantly working memory related abilities in a variety of tests (e.g. Spencer & Lal, 1983; Spencer et al., 1985). As the cognitive effects of scopolamine in human volunteers appear qualitatively similar to the cognitive decline in senile dementia, and as scopolamine is even used to test the functional integrity of the central cholinergic system in demented patients and the normal elderly (Sunderland et al., 1985; Richardson et al., 1985), the behavioural effects of scopolamine in animals could be considered a simple pharmacological model of senile dementia. The antagonist \( \beta \)-carboline ZK 93 426 antagonized the effects of scopolamine in the spontaneous alternation test (Sarter et al., 1988) which is assumed to measure working memory capacity at a rudimentary level (Warburton & Heise, 1972; Beninger et al., 1986). Similarly, the compound attenuated the behavioural impairments induced by scopolamine in a passive avoidance task (Jensen et al., 1987) and in a visual discrimination task analysed in accordance with the signal-detection theory (Jensen et al., 1987). Thus, the ability of ZK 93 426 to antagonize the behavioural effects of scopolamine seems to be a general pharmacological property of the compound.

**Effects in aged animals**

If carefully tested, senescent effects do not show dramatic behavioural impairments in comparison with mature young rats (Sarter & Markowitsch, 1983; Stephens et al., 1985; Sarter, 1987) in most tests of cognitive function. The frequently reported impairments of aged rats in passive avoidance tasks remain difficult to understand (Carew, 1970; Gold, 1986). Using a spatial delayed alternation task and the signal-detection task mentioned above, both impaired and normal aged rats showed relatively small but distinct impairments compared with the young animals (for details, see Sarter & Stephens, 1988; Stephens & Sarter, 1988; Jensen et al., 1987). Whereas ZK 93 426 significantly improved signal-detection performance of neither aged animals nor young animals, it improved delayed alternation behaviour in aged rats but impaired performance in young rats at a particular length of delay (20 s; Sarter & Stephens, 1988). The lack of effect of ZK 93 426 in the signal-detection task may have been a result of a near optimum performance of both groups before this test, so that no space for further improvement was available.

**Attenuation of basal forebrain lesion induced behavioural impairments**

Animals with lesions of the cholinergic neurons arising in the basal forebrain and innervating the cerebral cortex are considered to mimic some of the features of the cognitive impairments of dementia and of the pathoanatomy related to the cognitive decline in dementia. Ibotenic acid-induced basal forebrain lesions produced hyperactivity, decreased flexibility of choice behaviour, and a re-learning impairment in rats tested in a latent learning model based on an automated six-arm radial tunnel maze. ZK 93 426, administered before each session during acquisition, but not during re-learning of the maze, reduced locomotor hyperactivity, slowed exploratory speed during acquisition and, most impressively, attenuated the re-learning impairment of lesioned animals (M. Sarter & T. Steckler, unpublished work). No significant effects of the drug treatment were found in sham-lesioned control rats. Thus, treatment with ZK 93 426 seemed to improve learning in basal forebrain lesioned rats.

**GABA-benzodiazepine receptor-mediated modulation of cortical acetylcholine turnover**

ZK 93 426 improved behavioural performance in tests aimed at measuring learning and memory in animals showing deficits relative to controls as a result of either scopolamine administration, basal forebrain lesion or ageing. As the cognitive decline during ageing has also been attributed to the central cholinergic system (Bartus et al., 1987), it is speculated that the cognitive effects of ZK 93 426 are based on a GABAergic-cholinergic interaction.

Systemic administration of muscimol or diazepam, as well as direct intracranial injection of muscimol into the basal forebrain cholinergic region, have been demonstrated to antagonize cortical acetylcholine release as well as high affinity choline uptake (Casamenti et al., 1986; Petkow et al., 1983; Zsilla et al., 1976; Wenk, 1984). Furthermore, the cholinergic cell bodies in the basal forebrain seem to receive a direct GABAergic input in rat and man (Zaborszky et al., 1986; Ullig, 1988), and the substantia innominata of the rat contains a relatively high density of benzodiazepine receptors (Sarter & Schneider, 1988). Finally, ZK 93 426 showed an affinity for these receptors which was more than two times higher than that of diazepam (Sarter & Schneider, 1988). Taken together, these results are consistent with the hypothesis that the behavioural effects of ZK 93 426 are due to receptor-mediated modulation of substantia innominata-cortical cholinergic activity.

**Conclusions**

The characteristic properties of the pharmacological effects of ZK 93 426 in animals and human volunteers (Duka et al., 1987) show a considerable degree of qualitative similarities to the cognitive effects of cholinergic drugs (Warburton & Wenes, 1984), i.e. they seem to be related predominantly to stimulus processing. Such a viewpoint supports the idea that the nootropic effects of ZK 93 426 may be a result of increased cortical acetylcholine release. If this is true, it would be expected that compounds like ZK 93 426 should be able to improve some of the cognitive symptoms of, at least, early senile dementia (Procter & Bowen, 1988; Sarter et al., 1988).
Nootropics and metabolically active compounds in Alzheimer’s disease

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About 10% of people aged 65 years and over suffer from mild to moderate dementia (Hollister, 1985). Approximately 50–60% of this patient population are presently believed to suffer from senile dementia of the Alzheimer type (SDAT; Judd et al., 1986; Rogers et al., 1986). Alzheimer’s disease is, thus, the most common cause of behavioural alteration and cognitive reduction in the elderly. As the percentage of the total population aged over 65 is steadily increasing, SDAT will become an even more serious health problem. At present, pharmacological agents which stop the progression of SDAT have not been developed. Among the drugs which are most widely used to alleviate the symptoms are the nootropics and metabolically active compounds.

The prototype nootropic agent is piracetam (Fig. 1). The term was coined to describe the ability of this drug to improve integrative brain mechanisms associated with mental performance (Giurgea, 1982). The term nootropic does not describe the mechanism of action of the compound but rather the general pharmacological profile. The main features considered important for the classification of a nootropic agent are:

(i) The enhancement of learning and memory.

(ii) The facilitation of the flow of information between the cerebral hemispheres.

(iii) The enhancement of the general resistance of the brain to physical and chemical injuries.

(iv) The lack of usual psychological and general cardiovascular pharmacological activities.

This general pattern of pharmacological activity applies to many potential therapeutic agents, in this paper the term nootropic will refer solely to piracetam and piracetam-like compounds.

Abbreviations used: SDAT, senile dementia of the Alzheimer’s type; GABA, γ-aminobutyric acid; DHET, dihydroergotoxine.

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