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Pharmacologic and Clinicopharmacologic Properties of SDZ ENA 713, a Centrally Selective Acetylcholinesterase Inhibitor

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Among several clinically tested approaches to increase brain cholinergic activity, the acetylcholinesterase inhibitors (AChEIs) seem to represent the most promising substance class for treating Alzheimer's disease (AD). However, most compounds used so far in clinical trials lack brain selectivity, and their administration is accompanied by strong peripheral cholinergic or toxic effects. A cholinergic agent with an ideal profile should stimulate, directly or indirectly, central cholinergic receptors with an adequate duration of action and without influencing peripheral, particularly cardiovascular, systems. Physostigmine, a frequently used and very potent AChEI, has two serious disadvantages: its short biologic half-life and its unpredictable bioavailability after oral administration (Levy *et al.* 1986; Becker and Giacobini 1988).

We describe here some pharmacologic properties of a novel AChEI, SDZ ENA 713, that readily penetrates the central nervous system after parenteral and oral administration. This drug appears to have greater chemical stability and longer duration of action than does physostigmine. We also present first clinicopharmacologic data obtained with SDZ ENA 713 in healthy volunteers.

PHARMACOLOGIC METHODS

Activity of AChE was determined according to the method described by Ellman *et al.* (1961). Rat brain tissue was homogenized in cold 0.25 mM phosphate buffer, pH 7.4, containing 1% Triton X-100. After centrifugation, aliquots of the clear supernatant were used as enzyme source. AChE activity in different rat brain regions *ex vivo* was measured in similar extracts in which animals received various single doses of SDZ ENA 713 or physostigmine orally and subcutaneously, respectively, 30 minutes before sacrifice by decapitation.

Hippocampal electroencephalographic activity from anesthetized male Sprague-Dawley rats was recorded as described by Bevan (1984). The recording electrodes were implanted at the following coordinates (from bregma): A: −0.4 mm, L: 2.0 mm; and V: −2.5 mm.

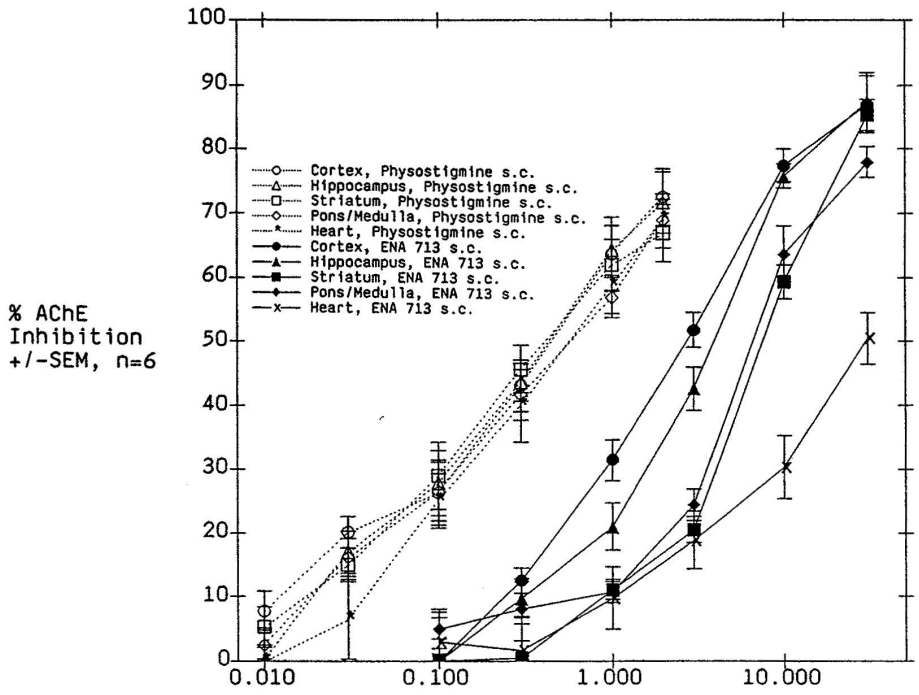

FIGURE 1. AChE inhibition by SDZ ENA 713 and physostigmine in rat brain and heart. *Horizontal axis*: Dose (μmol/kg) s.c. 30 min before sacrificing.

PHARMACOLOGIC RESULTS

ENA 713 inhibited AChE in a time-dependent manner. The compounds was found to be 100 times less potent than was physostigmine (Ki values ENA 713: 1-2 $\times$ 10^{-6} M; physostigmine: 1-2 $\times$ 10^{-8} M) *in vitro*, but the difference was reduced to a factor of 10 in *in vivo* experiments (FIG. 1). SDZ ENA 713 inhibited AChE in rat hippocampus and cortex (two brain regions primarily affected in AD) more potently than in other regions such as striatum and pons/medulla or than in the heart. This selectivity was not observed with physostigmine. A characteristic property of central muscarinic stimulation by either muscarinic agonists or AChEI is the induction of slow rhythmic activity (synchronization of theta waves) in the rat hippocampus (Bevan 1984). Intraperitoneal administration of SDZ ENA 713 to anesthetized rats induced a pronounced increase in the hippocampal theta rhythm (+120% with 0.8 mg/kg), a similar effect being obtained with physostigmine. Following oral administration of SDZ ENA 713, the effect was also pronounced (+170%). Up to a dose of 1.5 mg/kg intravenously (a dose inducing marked central cholinergic activation), SDZ ENA 713 showed no effects on circulatory parameters in the anesthetized cat (Enz *et al.* 1989).

FINDINGS IN HEALTHY HUMAN VOLUNTEERS

Eighty young male subjects took part in a study of the tolerability and pharmacodynamic effects of single rising oral doses of SDZ ENA 713. Eight groups of 10 subjects (7 on active medication, 3 on placebo in each group) received single rising oral doses

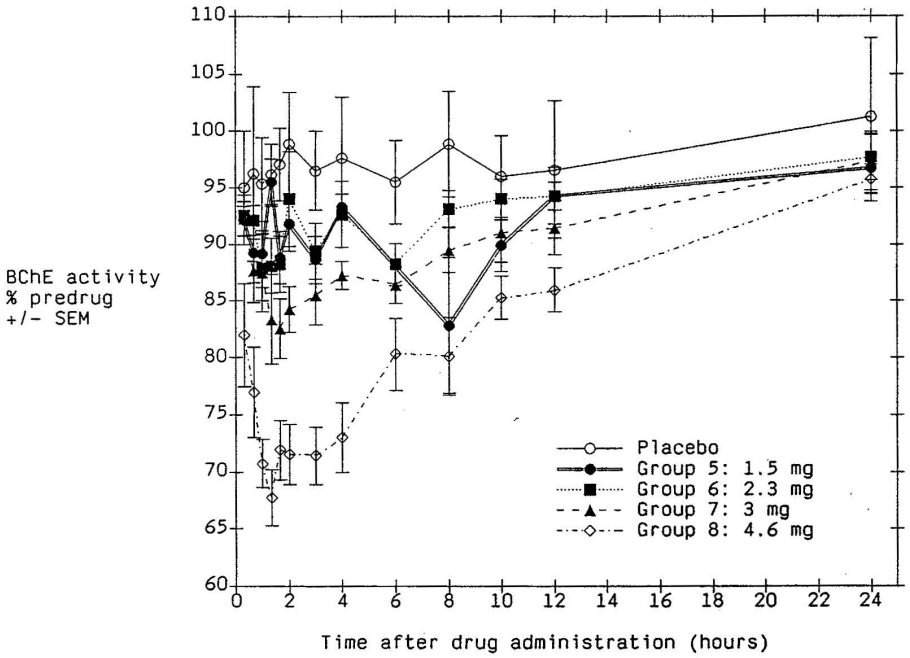

FIGURE 2. BChE activities in human plasma after single oral ENA 713 administration.

of 0.16, 0.30, 0.60, 1.0, 1.5, 2.3, 3.0, and 4.6 mg of SDZ ENA 713 or placebo. Tolerability up to the 3-mg dose was generally good. After the 4.6-mg dose, nausea, vomiting, headache, or dizziness was observed in four of seven subjects after active medication. However, peripheral cholinergic signs such as sweating and salivation were absent or minimal. Vital signs and routine hematologic and biochemical parameters were not significantly altered at any dose level.

Dose-dependent inhibition of plasma butyrylcholinesterase was observed with a duration of action of greater than 10 hours (FIG. 2). In a separate study, single doses of 1.3 and 2.0 mg were centrally active, inducing an increase in the density of rapid eye movements during REM sleep in healthy young volunteers. Therefore, the concept of SDZ ENA 713 as a centrally selective, long-acting acetylcholinesterase inhibitor is so far confirmed by experience in man. Subsequent experience with single and multiple dose administration in young and elderly volunteers and patients with AD have continued to support this concept. The compound is presently being tested as a symptomatic treatment for AD.

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