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Letters to the Editor

The effects of raubasine and dihydroergocristine on an age-related deficit in passive avoidance learning in rats

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A combination of dihydroergocristine and raubasine, 1:8 (w/w), has been shown to be effective in treating the symptoms associated with mental aging in man. Patients treated with the combination were significantly improved compared with placebo for all items of Israel's scale of intellectual vitality (power of recall, attention, power of expression, alertness, general vitality, verbal fluency and general memory) (Hugonot et al 1985).

We have evaluated the effects of the drug combination on the behaviour of rats with age-related cognitive deficits in a step-through passive avoidance task.

Experiments were performed with male Long-Evans rats (Janvier, France) aged 3–5 and 32 months (n = 10), housed in individual cages with food and water freely available.

The apparatus consisted of a white compartment (30 × 30 × 30 cm) connected by an opening (7 × 7 cm) to a black compartment (20 × 20 × 12 cm), with a grid floor. A (100 W) light was positioned centrally 50 cm above the base of the large compartment.

Initially each rat was placed in the bright compartment and after 30s the entrance to the dark compartment was opened (time 0) and the time taken for the rat to have four paws on the grid was recorded; at the same time the door was closed and a 2s shock was delivered. Immediately after the rat was returned to its home cage. Forty eight h later the delay in entering the dark compartment was again recorded to a maximum of 300 s. To evaluate the effects of the combination in 32 month old rats the shock was 1·2 mA at which level retention of the 5 month old rats was maximal (300 s): in treated young animals, a shock of 0·6 mA yielded behaviour comparable to that of the 32 month old rats.

The combination of dihydroergocristine and raubasine (Iskedyl, Pierre Fabre Médicament) was suspended in distilled water with four drops of Tween 80 and the suspension was injected (2 mL kg^{-1}) intraperitoneally 30 min before the initial trial. Controls were treated with vehicle.

All results were expressed as the mean ± s.e.m. and compared using a Kruskal-Wallis non-parametric one-way analysis of variance followed by a 2-tailed Mann-Whitney U-test.

The behaviour of young, and aged rats did not differ during the training period. During testing, however, 32 month old rats exhibited a significant decrease in retention of the inhibitory avoidance task when compared with young controls (−74%, $P < 0.002$) (Table 1). The drug combination had no effect on the latency in 3 month old rats (Table 2) but in 32 month old rats, a dose containing raubasine 28·8 and dihydroergocristine 3·6 mg kg^{-1} significantly increased the time taken to enter the dark compartment (+199%, $P < 0.05$). In the old rats, at half that dose the response was noticeable but not significant (+139%) (Table 1) (the number of 32 month old rats was insufficient to test other doses).

The combination has been shown to increase cerebral blood flow (Bailly et al 1974) which could indirectly improve memory and cognitive functions in aged animals and patients. On the other hand, the neurochemical properties of the two drugs may also be involved. The major activities of the combination can be summarized as a dopaminergic stimulation, a noradrenergic inhibition, a 5-hydroxytryptamine inhibition and a cholinergic stimulation (see review by Briley 1985).

The increase in the release of acetylcholine induced by the components (Markstein 1983) could attenuate an age-related cholinergic deficit. The dopamine agonist properties (D'Urso et al 1982) would also tend to alleviate an age-related dopaminergic deficit.

By its blockade of 5-HT_2 receptors (Briley 1985) and by reducing the synthesis and release of 5-HT (Briley & Moret 1986), the combination could also enhance learning and memory.

Dihydroergocristine has recently been shown to facilitate acquisition of active avoidance behaviour in a shuttle box paradigm and retention of passive avoidance responses in 26 month old rats (Drago et al 1988). To what extent the observed effects are due to the activity of one or other of the components requires further study.

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Table 1. Effects of acute administration (i.p.) of the combination (Dose 1 = 14·4 mg kg^{-1} of raubasine and 1·8 mg kg^{-1} of dihydroergocristine. Dose 2 = 28·8 mg kg^{-1} of raubasine and 3·6 mg kg^{-1} of dihydroergocristine) in 32 month old Long-Evans rats compared with 5 month old rats on single trial passive avoidance task (1.2 mA/2s). Mean ± s.e.m. of 10 rats.

		Step-through latency (s)	
Age (months)	Drug	Training	Testing
5	Control	11·1 ± 1·7	300
32	Control	13·0 ± 2·8	78·1 ± 37·2*
32	Dose 1	13·9 ± 2·0	186·3 ± 41·4
32	Dose 2	13·6 ± 1·9	233·6 ± 37·1†

* $P < 0.002$ compared with young control. † $P < 0.05$ compared with aged control.

Table 2. Effects of acute administration (i.p.) of the combination (Dose 1 = 14·4 mg kg^{-1} of raubasine and 1·8 mg kg^{-1} of dihydroergocristine. Dose 2 = 28·8 mg kg^{-1} of raubasine and 3·6 mg kg^{-1} of dihydroergocristine) in 3 month old Long-Evans rats on single trial passive avoidance task (0·6 mA/2s). Mean ± s.e.m. of 10 rats.

	Step-through latency (s)		
Drug	Training	Testing	
Control	10·4 ± 1·3	127·4 ± 47·0	
Dose 1	12·5 ± 1·9	125·3 ± 47·6	−2%
Dose 2	11·1 ± 2·2	100·9 ± 43·5	−21%

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Definitive IUPAC Recommendations

The following definitive recommendations on nomenclature, terminology, and symbolism have been published since January 1989:

1. Electrochemical corrosion nomenclature. Pure Appl. Chem. (1989) 61: 19
2. System for symbolic representation of reaction mechanisms. Pure Appl. Chem. (1989) 61: 23
3. Detailed linear representation of reaction mechanisms. Pure Appl. Chem. (1989) 61: 57
4. Definitions of terms relating to individual macromolecules, their assemblies, and dilute polymer solutions. Pure Appl. Chem. (1989) 61: 211
5. A classification of linear single-strand polymers. Pure Appl. Chem. (1989) 61: 243
6. Nomenclature for organic chemical transformations. Pure Appl. Chem. (1989) 61: 725
7. Definition of terms relating to crystalline polymers. Pure Appl. Chem. (1989) 61: 769
8. Nomenclature for automated and mechanised analysis. Pure Appl. Chem. (1989) 61: 1657
9. Nomenclature of steroids. Pure Appl. Chem. (1989) 61: 1783
10. Recommendations for EPR/ESR nomenclature and conventions for presenting experimental data in publications. Pure Appl. Chem. (1989) 61: 2195

Comments on these recommendations would be welcomed, addressed to the originating IUPAC Commission (for addresses see the appropriate issue of Pure Appl. Chem.), with copies to Dr Alan McNaught, Secretary, Joint Royal Society/Royal Society of Chemistry Panel on Chemical Nomenclature, Thomas Graham House, Science Park, Milton Road, Cambridge CB4 4WF, UK.