Conflict behaviour in rats for the evaluation of a homogeneous series of 3-hydroxybenzodiazepines: structure-activity relationships

M. BABBINI*, M. BARTOLETTI, F. DE MARCHI, M. GAIARDI & M.V. TORRIELLI

Institute of Pharmacology, University of Bologna, Italy

The conflict behaviour in rats according to Geller (Geller & Seifter, 1960) was employed to investigate the structure-activity relationship of a series of nine benzodiazepines substituted in the N_1 position (H, CH_3 or CH_2CH_2OH) and in the ortho position of the phenyl ring (H, F or Cl).

Rats previously trained to a conflict behaviour schedule in conventional Skinner boxes were used. For each compound four doses were tested using 5-6 animals per dose level. The effects upon both the punished and non-punished response rates were taken into account.

The actions of the same series of drugs upon exploratory activity, cortical EEG, metrazol-induced seizures and inclined screen test were also investigated to control the concordance of the conflict behaviour with other tests for central activity.

It was found that: (1) Substitution into N_1 position with a methyl group increases the anxiolytic potency of the compound while a longer chain (CH_2CH_2OH) reduces it. (2) Halogen subsitution in the ortho position of the phenyl ring very strongly enhances the anxiety-reducing action whatever the N_1 substitution may be. (3) Fluorine seems equivalent to chlorine in determining the anti-anxiety potency of the compounds. (4) The results of the conflict behaviour test correlate well with those obtained in the other tests.

Reference

GELLER, I. & SEIFTER, J. (1960). *Psychopharmacologia*, **1**, 482.

Sleep and hypothermic effects of clonidine in fowls

E. MARLEY* & G. NISTICO

Institute of Pharmacology, IInd Faculty of Medicine, Naples, Italy, and Department of Pharmacology, Institute of Psychiatry, De Crespigny Park, London SE5 8AF

Clonidine (2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride) induces sleep when given intravenously to cats and young chickens (Zaimis, 1970; Holman, Shillito & Vogt, 1971) and when given intraventricularly to rats (Holman *et al.*, 1971). In sheep and goats intraventricular clonidine lowered or elevated body temperature, depending whether ambient temperature was below or above thermoneutrality (Maskrey, Vogt & Bligh, 1970).

The following experiments were performed in adult fowls at thermoneutrality. Given into the *IIIrd cerebral ventricle*, clonidine (0.02-0.4 μmol) induced behavioural and electrocortical sleep (15-30 min) followed by drowsiness, chickens squatting or standing; body temperature declined up to 2.0°C with recovery in 2-4 hours. These phenomena resembled those produced by intraventricular noradrenaline, 0.5 μmol; much more marked than with noradrenaline, respiratory rate increased to 60-150 min for 15-40 min and there was wing abduction. Changes in comb temperature, which increased as much as 10.0°C during the decline in body temperature, were reciprocally related to changes in body temperature. Arousal elicited by dexamphetamine (20 μmol/kg i.p.) was antagonized and replaced by sleep after intraventricular clonidine (0.1-0.4 μmol). *Infused into the hypothalamus*, clonidine (0.02-0.16 μmol) induced behavioural and electrocortical sleep lasting 60 min; body temperature declined up to 1.8°C with recovery delayed to 7 hours. With larger doses (0.1 μmol or greater) respiratory rate was elevated and associated with wing abduction. These effects of intraventricular clonidine (0.05 μmol) were prevented (intraventricular doses) by phenoxybenzamine (0.25 μmol) and substantially reduced by phentolamine (0.05 and 0.75 μmol), but were unaltered by propranolol (0.25 μmol), methysergide (0.1 μmol), atropine (0.4 μmol), or by pretreatment with p-chlorophenylalanine methyl ester. These doses of antagonists lacked intrinsic effects except for atropine which elevated body temperature 2.0°C-2.5°C; intraventricular phentolamine 0.135 μmol and 0.27 μmol also elevated body temperature, evoked shivering and wing abduction, and increased respiratory rate. Hyperthermic effects of intraventricular phenoxybenazine, and to a lesser extent phentolamine, have been observed in cats (Feldberg & Saxena, 1971).

In conclusion, sleep, previously noted by other workers, following intravenous clonidine in chicks,