Sedation, stereotypy and the inhibition of drinking after administration of ET 495 in the rat

S.J. COOPER & C.T. DOURISH

Laboratory of Experimental Psychology, Sussex University, Brighton & Department of Psychology, Queen's University of Belfast, Belfast, BT7 1NN.

Piribedil (ET 495) is a dopamine-receptor activating agent (Corrodi, Farnebo, Fuxe, Hamberger & Ungerstedt, 1972), which induced behavioural stereotypy (Costall & Naylor, 1974; Creese, 1974), and produces turning behaviour in nigrostriatal-lesioned rats (Corrodi, *et al.*, 1972). ET 495 suppresses drinking elicited by either water deprivation or i.p. injection of hypertonic NaCl solution (Dourish & Cooper, 1978), which is consistent with a possible involvement of dopaminergic mechanisms in the control of thirst (Blundell & Latham, 1979). At low doses, dopamine-receptor agonists possess a 'paradoxical inhibitory action' (Carlsson, 1978), producing sedation in man (Angrist, Ain, Rotrosen, Gershon, Sachs & Halpern, 1977). We have conducted experiments to determine if low dose levels of ET 495 induce signs of sedation in the rat, and if the inhibition of drinking by ET 495 is solely secondary to the production of sedation, or stereotypy.

Male, adult, Sprague-Dawley rats (250–300 g) were housed individually in metal grill cages, and water was provided by a 50 ml calibrated burette mounted outside each cage. Piribedil methane sulphonate, dissolved in water, was administered to the rats by i.p. injection, 15 min before a 60 min observation period. The dose levels used were: 0.5, 1.25, 2.5, 5.0, 10.0, 20.0, 30.0 and 40.0 mg/kg. Each rat was tested once only.

At dose levels above 20.0 mg/kg, ET 495 induced marked behavioural stereotypy (repetitive sniffing in a fixed location, occasional gnawing episodes) in all animals. (Ten rats per dose level). Over the dose range, 0.5–20.0 mg/kg, all animals showed some signs of behavioural sedation (20 rats observed at each dose level) beginning within 30 min of the injection. The features, as they developed, were: restriction of movement to a single location, with occasional locomotor activity; stationary, with burst of yawning and/or body-stretching; motionless with eyes partially closed; sleep. The degree of sedation was dose-related. Control animals remained active over the same period.

During the 1 h observation period, control animals, deprived of water for 24 h, drank 5.02 ± 0.04 ml (mean $\pm$ s.e. mean) in the first 15 min, and 7.20 ± 0.37 ml by the end of the test. Water intake was reduced after injection of ET 495, 0.5–20.0 mg/kg, with a maximal depression occurring at 5.0 mg/kg (15 min intake = 0.84 ± 0.1 ml, $P < 0.005$). In an additional experiment, pretreatment with spiperone (5 or 10 μg/kg) completely blocked the inhibition produced by ET 495 (5 mg/kg). It seemed possible that any depression in water intake might be secondary to the induction of sedation. Hence in further experiments, water was only restored to the animals after all signs of sedation (or stereotypy, if present) had dissipated. Each drug-treated animal was matched with a control animal in terms of the time when water was returned (3.5–4.5 h post-injection). The intake in a matched control group was 10.75 ml in a 1 h test, but only 6.04 ml in a group injected with 20.0 mg/kg ET 495 ($t = 3.31$, 17 df, $P < 0.005$). Similarly, intake in a second control group was 13.50 ml, but only 8.13 ml in a group injected with 5.0 mg/kg ET 495 ($t = 3.09$, 5 df, $P < 0.025$). Hence, ET 495 appears to depress drinking, separately from the induction of sedation at low dose levels.

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