Stress-induced partial insomnia: a model for the evaluation of potential hypnotic compounds

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The testing of new hypnotics has usually been performed in normal animals (Babbini, Torrielli, Strumia, Gaiardi, Bartoletti & De Marchi, 1975). Logically, better assessment of efficacy would be to screen the drugs in insomniac animals. There are several published methods for the selective deprivation of different sleep states (Albert, Cicala & Siegal, 1970; Morden, Mitchell & Dement, 1967; Ogilvie & Broughton, 1976) but much of this work may be unsuitable for evaluation of drug activity for example, in the 'island technique' there is no facility for quantitating the reversal of the insomnia. This paper will describe a technique of inducing reversible insomnia which is readily and accurately quantitated and can be used for evaluation of hypnotic properties. Two benzodiazepines, namely RU 31158 [6-(ortho-chlorophenyl)-1,2-dihydro-2(N-methyl-piperazin-1-yl)-methylene-8-nitro-1H,4H-imidazo [1,2-a][1,4]benzo-diazepin-1-one methanesulphonate] (Taylor, 1976) and flunitrazepam, as well as phenobarbitone, morphine and chlorpromazine have been examined in this test.

Male Wistar CFHB rats (200–275 g) were used in the study in which the electrocorticogram (ECoG) and electromyogram (EMG) were automatically analysed to quantitate the sleep states (Johns, Piper, James, Birtley & Fischer, 1976). Following a 40 h acclimatisation period, an 8 h placebo treated control recording was performed. On the succeeding day, placebo or drug was given orally and the animals were stressed. The stress was induced by foot electroshock delivered through the EMG recording leads and the metal grid floor, 0.5 mA for 30 s every 30 min, 15 msec pulse width at 1 Hz. During the electroshock period the ECoG and EMG recording circuits were automatically interrupted by a two-way relay switch system. The results of the stress procedure on 10 animals was to significantly ($P \leqslant 0.05$) increase the arousal and slow wave sleep (SWS) I phases of the sleep cycle. There was a significant ($P \leqslant 0.05$) decrease in SWS II and paradoxical sleep throughout the eight hours.

RU 31158 (8 mg/kg, $n = 10$) and flunitrazepam (4 mg/kg, $n = 10$) were effective sleep inducing agents in this model. Both compounds restored the arousal and paradoxical sleep patterns to a control profile and partially restored the SWS II pattern, although RU 31158 was most active for the first 3 h and flunitrazepam reached peak activity on SWS II at four hours.

Phenobarbitone (50 mg/kg, $n = 10$) was active in suppressing the stress increased arousal. However, there was a significant ($P \leqslant 0.05$) increase in SWS I and a concomitant decrease in SWS II. Paradoxical sleep was suppressed. Chlorpromazine (8 mg/kg, $n = 10$) was ineffective as a sleep inducing compound. There was a significant increase only in SWS I at 2–4 h which reflects the action of chlorpromazine on normal animal EEG (Babbini, Gaiardi & Bartoletti, 1975). Morphine (17.2 mg/kg, $n = 10$) was ineffective in this model.

The results suggest that the stress-induced partial insomnia in the rat is a reliable model for screening potential hypnotic compounds. The two benzodiazepines, RU 31158 and flunitrazepam presented good hypnotic profiles whilst representative drugs from other major CNS categories were either only partially active or completely inactive.

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