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LETTERS TO THE EDITOR

Interaction between cerebral amines and 4-hydroxybutyrate in the induction of sleep

Little is known about the mechanism of action of short-chain fatty acids and their derivatives on sleep induction (Jouvet, 1967a). An action at the level of serotoninergic or noradrenergic reticular ascending systems is conceivable. Experiments concerning a possible conversion of 4-hydroxybutyrate to γ-aminobutyrate and vice versa (Della Pietra, Illiano & others, 1966; Mitoma & Neubauer, 1968; Roth & Giarman, 1969) and the effect of 4-hydroxybutyrate on cerebral glucose metabolism (Laborit, 1964; Godin, Mark & Mandel, 1968) have failed to answer this problem. The investigations of Gessa, Crabai & others (1966, 1968) have pointed out that intraperitoneal 4-hydroxybutyrate produces a rise of cerebral dopamine in rats and rabbits. Whether this is a coincident or a causal finding is still debatable.

To test if dopamine influences the hypnotic action of 4-hydroxybutyrate we gave L-dopa (the natural precursor of this amine) intraperitoneally to mice. Since fully hypnotic doses of 4-hydroxybutyrate proved to be convulsive in some animals we injected a reduced amount of the drug. Thirty min later the animals were injected by the same route with 4-hydroxybutryate. Controls received dopa followed by saline. To exclude any aspecific synergism we gave mice, similarly pretreated with dopa, a dose of pentobarbitone. Sleep onset and duration were judged by the loss and the return of righting reflex. Results are summarized in Table 1.

It is evident that dopa strongly enhanced the hypnotic effect of 4-hydroxybutyrate, whereas its influence on the action of pentobarbitone was minimal and not significant.

These results are of some interest as the administration of L-dopa alone has been shown to produce an increase in waking (Jouvet, 1967b).

Table 1. *Effect of a load of* L-dopa *on sleep induced by* 4-*hydroxybutyrate* (*γ-OH*) *and pentobarbitone*

No. of mice	Drug	Duration of sleep (±s.e.) (min)	% Asleep	Lag time (±s.e.) (min)
9	L-Dopa (50 mg/kg)	—	0	—
20	4-Hydroxybutyrate (500 mg/kg)	2 ± 0	10	8 ± 1
20	L-Dopa (50 mg/kg) + γ-OH (500 mg/kg)	27 ± 6*	40	8 ± 2
25	4-Hydroxybutyrate (750 mg/kg)	4 ± 1	56	6 ± 1
25	L-Dopa (50 mg/kg) + γ-OH (750 mg/kg)	34 ± 6*	68	7 ± 1
12	Pentobarbitone (38 mg/kg)	30 ± 7	58	
12	L-Dopa (50 mg/kg) + pentobarbitone (38 mg/kg)	40 ± 10	58	
12	Pentobarbitone (30 mg/kg)	—	0	
12	L-Dopa (50 mg/kg) + pentobarbitone (30 mg/kg)	—	0	

* $P > 0{\cdot}01$, *t*-test

The purpose of these experiments was to check the hypothesis that a direct interaction between fatty acid molecule and chemical transmitters of noradrenergic systems can account for sleep induction (Rizzoli & Galzigna, 1969). The present experiments do not exclude such an hypothesis.

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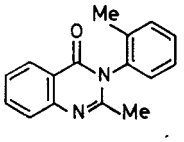
Fluorimetric assay of methaqualone in plasma by reduction to 1,2,3,4-tetrahydro-2-methyl-4-oxo-3-*o*-tolylquinazoline

There is a need for a method of assay of therapeutic plasma levels of the hypnotic drug methaqualone (I). Several indirect methods of estimating the drug necessitate acid or alkaline hydrolysis to diazotizable amines (Maggiorelli & Gangemi, 1964; Nakano, 1964), but these lack specificity. Ultraviolet spectrophotometry offers more attractive quantitative procedures (Akagi, Oketani & Takada, 1964; Lawson & Brown, 1967), but the sensitivity is restricted by interference from biological blanks.

The structural resemblance between the dihydro-derivative of methaqualone (II) and anthranilic acid (III), an efficient fluorophor, suggested that a fluorimetric assay might be developed for methaqualone if a suitable reducing agent could be found. Okumura, Oine & others (1968) reduced some quinazolinone hydrochlorides with sodium borohydride, but the free bases were resistant to this reagent except under conditions which led to ring scission. We have found, however, that lithium borohydride is effective in reducing both free methaqualone and its hydrochloride to the tetrahydroquinazolinone



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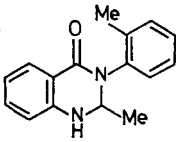

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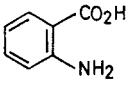

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