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LETTERS TO THE EDITOR

A reduced rate of turnover of brain noradrenaline during pentobarbitone anaesthesia

When using the specific tyrosine hydroxylase inhibitor, α-methyltyrosine methylester (H44/68) in the barbiturate-anaesthetized rat, Corrodi, Fuxe & Hökfelt (1966) demonstrated a reduced turnover of dopamine in the brain. However, the effect on brain noradrenaline was small, if any.

Brain noradrenaline disappears about twice as rapidly after dopamine β-hydroxylase inhibition as after inhibition of tyrosine hydroxylase (Goldstein & Nakajima, 1968; Bapna, Neff & Costa, 1970; Corrodi, Fuxe & others, 1970; Persson & Waldeck, 1970a). This observation as well as others led to a suggestion that there was an interaction between dopamine- and noradrenaline-containing neurons in the brain (Persson & Waldeck, 1970b). We therefore found it necessary to reinvestigate the effect of barbiturates on the rate of disappearance of noradrenaline after inhibition of its synthesis using H44/68 or the specific inhibitor of dopamine β-hydroxylase, bis(4-methyl-1-homopiperazinylthiocarbonyl)-disulphide (FLA-63) (Florvall & Corrodi, 1970, Svensson & Waldeck, 1969). This inhibitor appears not to have amine-releasing properties of its own (Andén & Fuxe: unpublished observations).

Female mice, about 20 g, kept at an ambient temperature of 30° were randomly grouped six by six. Pentobarbitone sodium (60 mg/kg, i.p.) was given alone or followed 15 min later by either H44/68 (200 mg/kg, i.p.) or FLA-63 (40 mg/kg, i.p.). Animals receiving either of the inhibitors alone were run in parallel, with untreated mice as controls. The animals were decapitated 2 h after the inhibitor had been given or 2 h 15 min after pentobarbitone. Noradrenaline in the brain was measured according to Bertler, Carlsson & Rosengren (1958).

Since 60 mg/kg of pentobarbitone was not sufficient to keep the animals sedated throughout the experiment, another dose regimen was introduced in the subsequent

Table 1. *The effect of pentobarbitone on the disappearance of noradrenaline from the mouse brain after inhibition of its synthesis.* Pentobarbitone was given either alone or 15 min before an injection of an inhibitor of tyrosine hydroxylase (H44/68) or of dopamine β-hydroxylase (FLA-63). In some experiments repeated doses of pentobarbitone were given. Mice receiving either of the inhibitors alone were run in parallel. Untreated animals served as controls. Two h after the synthesis inhibitor had been given, or 2 h 15 min after pentobarbitone administration, the animals were killed and noradrenaline in the brain determined. For time and dose schedules see text. Shown are the means ± s.e. in μg/g of three experimental groups each comprising 6 animals.

Pentobarbitone dosage mg/kg	Control	Pentobarbitone	H44/68	Pentobarbitone +H44/68	FLA-63	Pentobarbitone +FLA-63
60	0·52 ±0·047	0·47 ±0·026	0·32 ±0·009	0·31 ±0·012	0·19 ±0·006	0·22 ±0·009
80+20+20	0·53 ±0·047	0·58 ±0·040	0·34 ±0·031	0·38 ±0·023	0·18 ±0·007	0·34* ±0·024
80+20+20+20	0·48 ±0·032	0·56 ±0·019	0·38 ±0·038	0·35 ±0·107	0·18 ±0·013	0·38** ±0·017

* $P < 0{\cdot}01$. ** $P < 0{\cdot}001$ with respect to FLA-63 alone.

two experiments. An initial dose of 80 mg/kg was followed either by two further injections of 20 mg/kg given at intervals of 45 min, or three injections of 20 mg/kg given at intervals of 30 min. In these two experiments, animals receiving the synthesis inhibitors alone were given saline intraperitoneally to compensate for the possible dilution of the inhibitor caused by the repeated injections of pentobarbitone. Only the last mentioned dose regimen heavily sedated the animals throughout the experiment.

As in previous experiments, noradrenaline disappeared twice as rapidly after FLA-63 as after H44/68 (Persson & Waldeck, 1970a) (Table 1). Pentobarbitone, given alone, had no significant effect on brain noradrenaline. Nor did it change the rate of disappearance of the amine after H44/68 in any of the experiments. In a single dose, it also failed to change the rate of disappearance of noradrenaline after FLA-63. When two or three repeated injections of pentobarbitone were given, however, the decrease in noradrenaline brought about by FLA-63 was markedly inhibited (P <0·01 and 0·001 respectively).

H44/68 and FLA-63 in the doses used appear to inhibit the synthesis of noradrenaline equally well (cf. Svensson & Waldeck, 1969, 1971). Thus, the differences in the rate of disappearance of noradrenaline observed after the respective inhibitors may reflect differences in the level of activity of the noradrenaline-containing neurons, indicating an interaction between dopamine and noradrenaline-containing neurons in the brain (Persson & Waldeck, 1970b).

During pentobarbitone anaesthesia the activity of the dopamine-containing neurons is reduced as revealed by H44/68 (Corrodi & others, 1966). Does this reduction cause a change in the activity of the noradrenaline-containing neurons according to the interaction hypothesis? Using H44/68 this may be masked by the depletion of dopamine brought about by H44/68, thereby causing an impaired transmission. With FLA-63, which leaves the dopamine intact, a decreased rate of disappearance of noradrenaline after pentobarbitone was observed. This effect was more pronounced under a deep rather than a light anaesthesia.

It thus appears that during pentobarbitone anaesthesia the level of activity not only of the dopamine-containing but also of the noradrenaline-containing neurons is diminished.

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