Depression of Norepinephrine and 5-Hydroxytryptamine in the Brain by Benzoquinolizine Derivatives

Abstract. The effects of two benzoquinolizine derivatives on the 5-hydroxytryptamine and norepinephrine content of the brain of mice, and some pharmacological actions, are described. Certain central effects (such as sedation and narcosis potentiation) of benzoquinolizine derivatives and possibly of *Rauwolfia* alkaloids may be due to changes of norepinephrine metabolism rather than to changes of 5-hydroxytryptamine metabolism in the brain.

Reserpine and certain benzoquinolizine derivatives cause a marked depression of norepinephrine and 5-hydroxytryptamine levels in the brain of various animal species (*1*). The effects include sedation as well as potentiation of ethanol and barbiturate narcosis. It has been postulated that a causal connection exists between the pharmacological action of the afore-mentioned drugs on the central nervous system and their influence on monoamine metabolism (*2*). However, it is difficult to determine which change in the endogenous monoamines in the brain (norepinephrine or 5-hydroxytryptamine) is more important for the central effects of the drugs.

The benzoquinolizine derivatives investigated up to now have had almost equal effects, with regard to amount of depletion and duration of action, on norepinephrine and 5-hydroxytryptamine in the brain. Certain *Rauwolfia* alkaloids cause more marked norepinephrine than 5-hydroxytryptamine depression (*3*). Experiments with 3,4-dihydroxyphenylalanine and 5-hydroxytryptophan in animals pretreated with reserpine suggested that changes in norepinephrine levels might be more important than changes in 5-hydroxytryptamine levels (*4*).

Recently two benzoquinolizine derivatives (Fig. 1) (*5*) have been found to affect the brain content of 5-hydroxytryptamine in mice almost equally but the brain content of norepinephrine differently (Fig. 2). The average dose necessary to depress the 5-hydroxytryptamine content to about 50 percent of its original value (ED_{50}) was 2 mg/kg for compound I and 3 mg/kg for compound II. Maximum 5-hydroxytryptamine depression was reached in 1 hour, full recovery in about 6 hours, after administration of either of the compounds. The norepinephrine content, however, became markedly more depressed after administration of compound I than it did after administration of compound II. The ED_{50} for norepinephrine depression was about 5 times higher for compound II than for compound I.

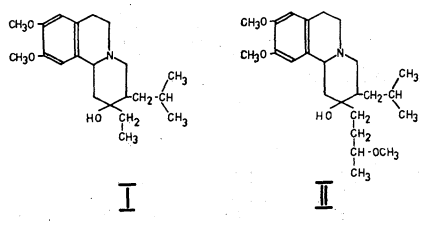

Fig. 1. Benzoquinolizine derivatives.

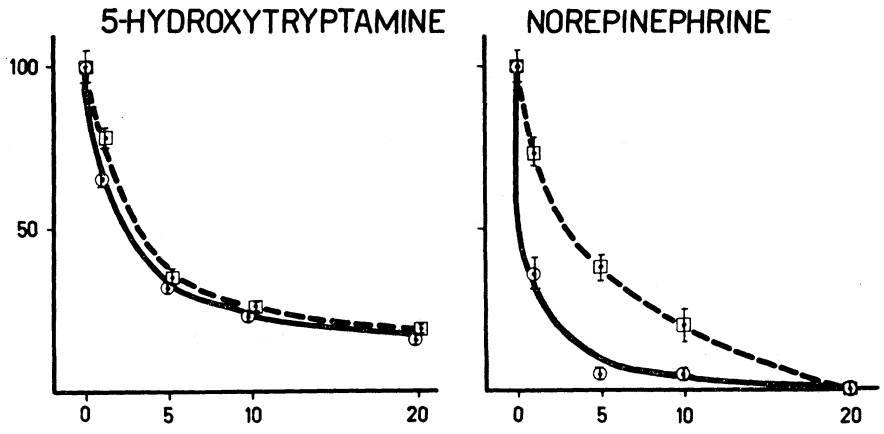

Fig. 2. 5-Hydroxytryptamine and norepinephrine content of the brains of mice after intraperitoneal administration of the benzoquinolizine derivatives I and II. Abscissa: dose (in milligrams per kilogram); ordinate: 5-hydroxytryptamine and norepinephrine content, respectively, as percentage of controls; solid lines, compound I; dotted lines, compound II. Each point represents the average of 6 to 27 determinations. For each determination the brains of five mice were pooled. Vertical lines, standard deviation. 5-Hydroxytryptamine and norepinephrine were determined by spectrophotofluorometric methods (*6*). The oxidation of norepinephrine was carried out with potassium ferricyanide. The blanks consisted of half the final extracts of each sample; no ascorbic acid was added before addition of the potassium ferricyanide. In the 5-hydroxytryptamine method only a reagent blank—no tissue blank—was subtracted. Interference of compounds I and II with the fluorescence of 5-hydroxytryptamine and norepinephrine could be excluded by experiments in which the compounds were added to the brain homogenates.

The pharmacological action of compounds I and II on the central nervous system of mice was also different. Compound I, in doses between 1 and 5 mg/kg, had a marked sedative effect. Furthermore, 5 mg of compound I per kilogram, injected 1 hour prior to administration of 4 g of ethanol per kilogram, prolonged the sleeping time to 110 ± 12 minutes. After administration of ethanol alone (4 g/kg) the average duration of sleep was 1 minute. A dose of 5 mg of compound II per kilogram had but a slight sedative effect. The period of ethanol-induced sleep was prolonged to 7 ± 3 minutes only.

Thus the pharmacological effects of compounds I and II on the central nervous system may possibly be related to the depression of norepinephrine but probably not to that of 5-hydroxytrptamine.

A. Pletscher
H. Besendorf
K. F. Gey

Medical Research Department,
F. Hoffmann-La Roche and Company,
Basle, Switzerland

References and Notes

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