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THE RESPIRATORY STIMULANT ACTION OF OCTYLAMINES

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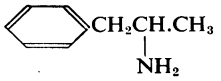
Most of the work on the pharmacology of octylamine has been done in connexion with the pressor effects of aliphatic amines. Barger and Dale (1910) found that a comparison of the pressor activity of octylamine, and other members of the series, was difficult because of their cardiac depressant effects. There was no doubt, however, that octylamine had less pressor activity in spinal cats than heptylamine, which in turn was less active than hexylamine. Swanson and Chen (1946) observed that 1-amino-octane did not increase the blood pressure of pithed dogs ; 1 mg. of 2-amino-octane, however, caused a rise in pressure equivalent to 0.5 μg. adrenaline. The respiratory stimulant action of 2-amino-alkanes in dogs under sodium pentobarbitone was observed by Alles (1946), who found that 2-aminoheptane stimulated the respiration more than hexylamine, 2-aminohexane, or 2-aminopentane. Alles also reported that 2-aminoheptane was the most active pressor agent in his series. Charlier (1951) showed that the respirations of dogs under chloralose were stimulated by 2-amino-6-methylheptane and that the stimulation lasted for more than sixty minutes.

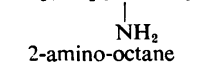
During a preliminary investigation of the pharmacological action of 1-amino-octane, it was observed that this amine, when injected into cats under sodium pentobarbitone, lightened the anaesthesia and resulted in deeper and more rapid respirations. This analeptic action of 1-amino-octane appeared to be great enough to warrant further investigation. Experiments were therefore carried out to compare the respiratory stimulation produced by 1-amino-octane with that by amphetamine. To complete the series, the analeptic activity of 2-amino-octane was also assessed. Amphetamine was chosen as a standard for comparison for two reasons : (1) because it is a useful antidote in barbiturate poisoning (Freireich and Landsberg, 1946 ; Nabarro, 1950) and (2) because a comparison was indicated between the pharmacological action of an aromatic amine and an aliphatic amine with a similar number of carbon atoms per molecule. This comparison would show whether a benzene ring is a necessary part of the molecular structure for optimum respiratory stimulation.



Amphetamine

$CH_3(CH_2)_7NH_2$

1-amino-octane



2-amino-octane

METHOD

The respiratory stimulant activity of these compounds was determined in rabbits in which the respirations had been depressed by 10 mg. sodium pentobarbitone, repeated when necessary to slow the rate and decrease the depth of respiration. The test drug was injected intravenously, and the changes in respirations were recorded on a smoked drum by Gaddum's (1941) method. A tracheal tube equipped with inlet and outlet valves was used. The inlet valve was connected by plastic tubing to a glass T-piece, one arm of which led to a large tambour and lever, and the other arm to one hole in the stopper of a 2-litre bottle. A capillary tube inserted through a second hole in the stopper restricted the entry of air into the bottle. Each inspiration by the animal momentarily decreased the pressure in the system and caused a downward excursion of the lever, the length of the swing being related to the amount of air inspired (Fig. 1). By repeating the dose of sodium pentobarbitone and by allowing adequate intervals between injections, it was possible to attain similar control levels of anaesthesia, and reproducible responses to the test drugs. Eight rabbits were used to compare amphetamine and 2-amino-octane and eight to compare amphetamine and 1-amino-octane. In each experiment the increase in respiratory rate produced by random doses of 2.5, 5.0, and 10 mg. amphetamine sulphate, and 2.0, 4.0, and 8.0 mg. of the aliphatic amine under test, was determined. The injections of 1-amino-octane and 2-amino-octane were dilutions of a 7 per cent (v/v) solution made by the addition of 0.7 ml. amine, 0.7 ml. water, 0.34 ml. HCl (conc.), and, when these were dissolved, water to 10 ml. The solutions injected had a *p*H of 7.1.

RESULTS

1-Amino-octane and 2-amino-octane (2.0–8.0 mg.) and amphetamine (1.5–6.0 mg.) increased the respiratory rate of rabbits and cats in which the breathing had been depressed by sodium pentobarbitone (Fig. 1). When adequate intervals were allowed

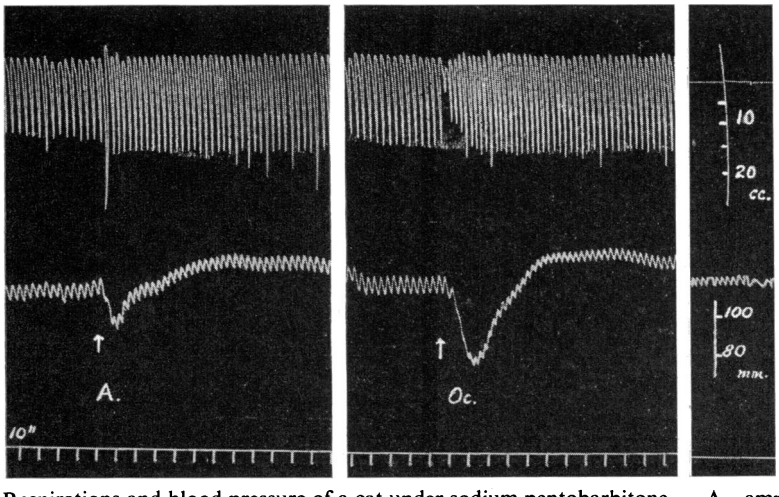


FIG. 1.—Respirations and blood pressure of a cat under sodium pentobarbitone. A = amphetamine sulphate, 5 mg. Oc = 1-amino-octane, 4 mg.

between injections, the three doses of amphetamine and test solution could be made into the same rabbit. The resulting increase in respiratory rate was a manifestation of greater pulmonary ventilation. Although occasionally the depth of respiration

decreased after the injection of these amines, this decline was only transient, and the volume of gas moved into and out of the lungs per minute was always increased. Within this range of doses, the duration of respiratory stimulation was from 10 to 20 min. for each substance.

The changes in respiratory rate produced by the three doses of each amine in terms of percentage increase of the depressed rate were computed in an analysis of variance as applied to graded response assays (Bliss and Marks, 1939). It was found that there was a linear relationship between the percentage increase in respiratory rate and the log dose of each amine (Fig. 2), and that the lines comparing amphet-

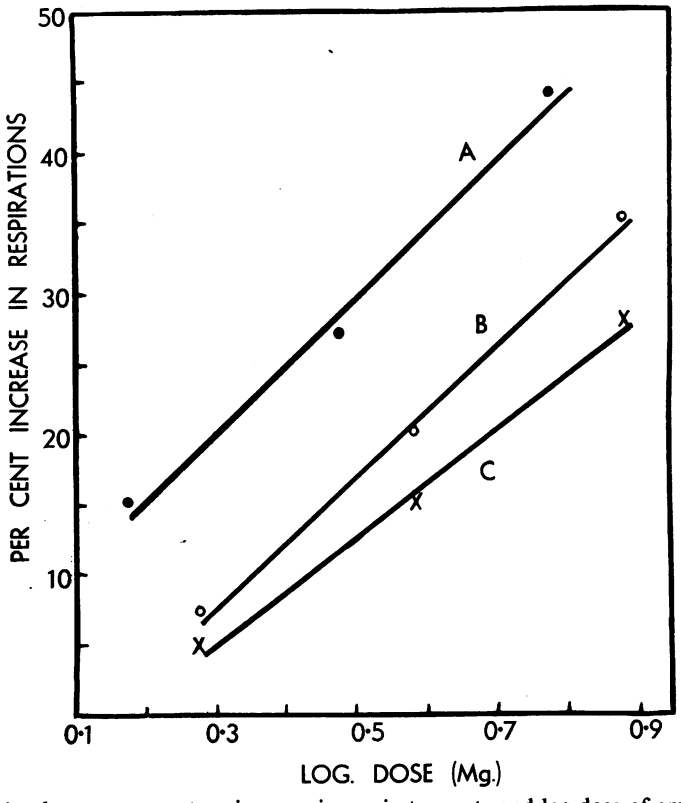


FIG. 2.—Relation between percentage increase in respiratory rate and log dose of amines in rabbits under sodium pentobarbitone. A, amphetamine; B, 2-amino-octane; C, 1-amino-octane. Each point is the mean of eight observations.

amine and 2-amino-octane and similarly the lines comparing amphetamine and 1-amino-octane did not differ significantly in slope. In eight rabbits, the ratio of potencies (with standard error) of amphetamine to 2-amino-octane was 1.84 ± 0.22. In eight additional rabbits the ratio of potencies of amphetamine to 1-amino-octane was 2.51 ± 0.25.

Mechanism of action.—The respiratory stimulant effect of 1-amino-octane, like that of amphetamine, was present after the nerves to the carotid body had been cut.

Both 1-amino-octane and 2-amino-octane increased the respiratory rate of rabbits in which breathing was depressed by morphine sulphate. The action of these amines therefore appears to be due to a direct stimulation of the respiratory centre under the influence of medullary depressant drugs.

Cardiovascular action.—1-Amino-octane and 2-amino-octane had less stimulant activity than amphetamine on the isolated rabbit heart perfused by the Langendorff method (Table I). The coronary outflow, however, was usually increased by 1-amino-octane. In rabbits under sodium pentobarbitone, 1-amino-octane and 2-amino-octane caused a transient fall in blood pressure followed by a slight, more prolonged increase in pressure. Alles (1946) found that the initial depressor effect of 1-amino-octane was not prevented by equal molar amounts of atropine.

TABLE I

RESPONSES OF PERFUSED RABBIT HEARTS TO AMINES

Amine	Doses	Number of hearts		
		Total	Increased rate	Coronary flow increased
Amphetamine	20–120 μg.	10	8	5
1-amino-octane	30–150 μg.	12	4	11
2-amino-octane	40–150 μg.	5	2	3

Toxicity studies.—The acute toxicities of these substances by the intravenous route were determined in adult, white mice (Table II). Although the LD50s of 1-amino-octane and 2-amino-octane were slightly larger than that of amphetamine, the therapeutic ratios were still less than that of the aromatic amine. After several days, daily subcutaneous injections of 8 mg. 1-amino-octane into rats caused necrosis of the tissue at the site of injection and the rats failed to gain weight, but no other toxic signs appeared.

TABLE II

Drug	Equiactive doses mg.	LD50 mg./kg.	Therapeutic ratio
Amphetamine	2.6	16	6.2
1-amino-octane	6.3	18	2.9
2-amino-octane	4.7	23	4.9

DISCUSSION

Several methods of assessing the amount of respiratory stimulation produced by a drug have been reported previously. These have been reviewed by Thorp (1947), who also described a method in which a comparison of respiratory analeptics was made by finding the doses required to restart the respirations of guinea-pigs anaesthetized with barbiturates. In this way the action of a substance on respiration could be shown independent of any awakening effect. The method used in the present study measured the direct action of a substance on respiration, and gave quantitative data suitable for a graded response assay of respiratory stimulant activity.

The observation that amphetamine was more effective than 1-amino-octane and 2-amino-octane in restoring depressed respirations to normal indicated that the presence of a benzene ring in an amine may be necessary for optimum analeptic activity. It was interesting to find, however, that aliphatic amines possessed as much stimulant activity as they did. Because they were found to have as long a duration of action as amphetamine and were less toxic, it is suggested that 1-amino-octane and 2-amino-octane may have a place in the treatment of some cases of respiratory depression. An analeptic should increase the circulation so that the removal of the substances which are depressing the vital centres is hastened. Of the drugs used in this study, amphetamine was the most active cardiovascular stimulant, although it was less effective than 1-amino-octane in dilating the coronary vessels. In man, 2-aminoheptane and 2-methylaminoheptane were reported to be active circulatory stimulants by Roma-Vega and Adriani (1944), who found that they were effective vasopressor agents in combating hypotension during spinal anaesthesia.

SUMMARY

1. In rabbits and cats with breathing depressed by sodium pentobarbitone, 1-amino-octane and 2-amino-octane increased the rate of respiration and the volume of gas moved in and out of the lungs per minute.

2. The ratio of analeptic activity of amphetamine to 1-amino-octane in rabbits was 2.51 ± 0.25, and of amphetamine to 2-amino-octane 1.84 ± 0.22.

3. Although 1-amino-octane and 2-amino-octane were less toxic than amphetamine, the therapeutic ratio was still in favour of amphetamine as a respiratory stimulant.

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