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Some pharmacological effects of 1,2,3,4-tetrahydro-2-naphthylamine (β-tetra) and its secondary *N*-alkyl derivatives

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Some effects of 1,2,3,4-tetrahydro-2-naphthylamine (β-tetra, β-tetrahydronaphthylamine, 2-aminotetralin) and four of its secondary *N*-alkyl derivatives on blood pressure in the cat and in the pithed rat are described. Pressor responses were obtained with β-tetra in both preparations. The introduction of an *N*-methyl group to form 1,2,3,4-tetrahydro-2-naphthylmethylamine led to a decrease in pressor potency in both species. The substitution of higher alkyl groups yielded compounds which were depressor in the cat and had markedly reduced pressor potency in the pithed rat. Increases in substituent chain length resulted in slight decreases in adrenaline-blocking potency and slight decreases in the tendency of the compounds to depress breathing. Experiments with β-tetra in reserpine-treated, adrenalectomized and hexamethonium-treated animals led to the conclusion that the pressor effect of 1,2,3,4-tetrahydro-2-naphthylamine is mediated by an action at the sympathetic neuron resulting in the release of noradrenaline.

THE compound β-tetra was first prepared by Bamberger & Müller (1888) and its pharmacological properties have since been extensively studied. Bovet and colleagues (Bovet, Bovet-Nitti & others, 1951; Bovet, Bovet-Nitti & Longo, 1952; Bovet, Sollero & Marotta, 1952; Bovet & Virno, 1952; Bovet, 1959) synthesized and examined some pharmacological actions of the *N*-methyl, *N*-dimethyl, *N*-ethyl and *N*-diethyl derivatives of β-tetra. They reported that these drugs had sympathomimetic actions and also possessed anti-adrenaline activity. The effects of 1,2,3,4-tetrahydro-2-naphthylamine (β-tetra, β-tetrahydronaphthylamine, 2-aminotetralin) and of some secondary *N*-alkyl derivatives on the blood pressure, respiration and pressor responses to adrenaline in the cat are now described. Pressor potencies of the compounds in the pithed rat preparation (Shipley & Tilden, 1947) have also been examined, so too has the mechanism of the pressor action of β-tetra. The compounds used were prepared by Craig, Moore & Ritchie (1959).

Experimental

METHODS

Cats of either sex (1·5–4 kg) were anaesthetized with intravenous chloralose (80 mg/kg) after induction with ether. Tracheal cannulation was such that respiratory movement could be recorded by the method of Gaddum (1941), or artificial respiration could be applied if needed. Blood pressure was measured via a cannula in a carotid artery by a mercury manometer. Drugs were administered into a cannulated vein.

In some experiments with β-tetra, cats were made spinal by the method of Burn (1952) and maintained by artificial respiration. Some cats were

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treated with 3 to 4 mg reserpine in 20% ascorbic acid, injected intraperitoneally, on each of 2 days and used on the 3rd day.

The experimental procedure for cats was as follows: adrenaline (5–40 μg) was injected intravenously at regular intervals, usually of 7–12 min. When the mean resting blood pressure was steady and responses to adrenaline were constant, β-tetra or one of its derivatives was injected intravenously. Progressively increasing doses were given at intervals of at least 20 min during which the regular injections of adrenaline were continued.

Blood pressure in pithed rats prepared as described by Shipley & Tilden (1947) was recorded with a Statham P23Db pressure transducer and ink-writing recorder (Pennefather & Rand, 1960). Rats received 1 mg atropine/100 g subcutaneously 20 min before use. In some experiments heart rate was also recorded.

The compounds used were: 1,2,3,4-tetrahydro-2-naphthylamine hydrochloride (β-tetra) and the *N*-methyl-(methyl β-tetra), *N*-ethyl-(ethyl β-tetra), *N*-n-propyl-(propyl β-tetra), and *N*-n-butyl-(butyl β-tetra) 1,2,3,4-tetrahydro-2-naphthylamine hydrochlorides.

Results

CATS

Each compound was given in a dose of 0·5 mg/kg to at least 4 cats. The primary amine, β-tetra, caused large pressor effects (45–80 mm Hg). Methyl β-tetra had decreased pressor potency (30–45 mm Hg). The effects of both drugs lasted 10–20 min. Tachyphylaxis occurred when subsequent equal or larger doses of either drug were given. Ethyl and propyl β-tetra had pronounced depressor effects (−20 to −45 and −40 to −55 mm Hg respectively) which often lasted for more than 1 hr. Subsequent injections of ethyl-β-tetra often produced pressor effects. Fig. 1 shows a record of blood pressure from a cat given propyl β-tetra. Butyl β-tetra was a less potent hypotensive agent (−10 to −25 mm Hg) than propyl β-tetra and its effect was relatively short-lived.

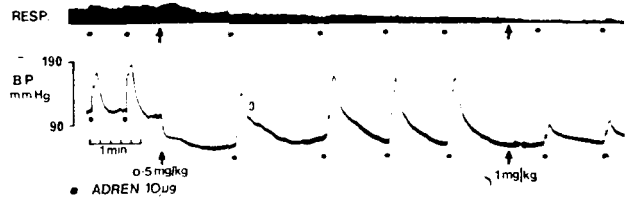

FIG. 1. Record of blood pressure (lower trace) and breathing (upper trace) in a cat anaesthetized with chloralose. Pressor responses at spots were produced by injection of adrenaline 10 μg. Propyl β-tetra (↑) lowered the blood pressure and depressed breathing. Subsequent response to injections of adrenaline were prolonged. A second dose of propyl β-tetra, 1 mg/kg, given while the blood pressure remained low, further depressed breathing: responses to adrenaline were reduced.

Anti-adrenaline activities of the compounds were compared by determining the dose (A) of each that caused 100% abolition of the pressor response to adrenaline. The respiratory depressant effects of the compounds were compared by determining for each the dose (R) that caused cessation of breathing. These doses (in μmole/kg) were: β-tetra A 10 (5–11), R 15 (5–22); methyl β-tetra A 10 (10), R 13 (10–20); ethyl β-tetra A 23 (7–48), R 26 (2–49); propyl β-tetra A 35 (22–44), R 26 (9–44); butyl β-tetra A 20 (8–21), R 20 (8–41). Thus potency in blocking pressor responses to adrenaline was similar with β-tetra and its methyl derivative but then showed a fall to the propyl derivative, rising again with the butyl compound. In some experiments with β-tetra and methyl β-tetra, adrenaline 'reversal' was observed after giving a number of doses.

The primary amine and its methyl derivative caused most depression of breathing with successive reductions from ethyl to propyl. Butyl-β-tetra showed an increased effect. Although β-tetra and methyl β-tetra had the most depressant activity, they caused least respiratory depression in doses which were effective in blocking the pressor effect of adrenaline. Thus, their R/A ratios were 1·5 and 1·3, whereas, those for the ethyl and propyl derivatives were 0·8 and 0·7 respectively.

RATS

Compared on a per kilogram basis the compounds were approximately ten times more potent as pressor agents in the pithed rat than in the cat and tachyphylaxis and cross-tachyphylaxis were not observed. All compounds were pressor, the relative potencies being: β-tetra 85–105; methyl β-tetra 40–65; ethyl β-tetra 1·5–2·5; propyl β-tetra 1·2–3; butyl β-tetra 1·2–2·3. In other experiments, the potency of β-tetra was compared with that of (±)-amphetamine and that of tyramine. Amphetamine and β-tetra were approximately equipotent and both were about 65% as potent as tyramine. In Fig. 2, a record of blood pressure in a

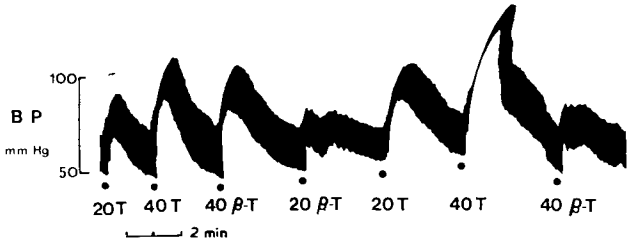

FIG. 2. Record of blood pressure of pithed rat. β-Tetra (40 μg) produced a pressor response intermediate in height between responses to tyramine (T) 20 and 40 μg. Subsequent responses to tyramine were larger than before β-tetra was given, whereas the response to a second injection of β-tetra was smaller.

pithed rat is shown. Injections of tyramine and of β-tetra were alternated at fairly short intervals. The responses to tyramine became larger with each successive injection while those to β-tetra became smaller. If injections of tyramine were discontinued there was no significant reduction

in the size of responses to repeated injections of β-tetra. The relative absence of tachyphylaxis to the actions of the compounds, and of any noticeable cross-tachyphylaxis between them suggests that the pithed rat preparation is suitable for the comparison of pressor activities of drugs of this type.

ACTION OF β-TETRA IN RESERPINE-TREATED ANIMALS

Cats. The pressor action in spinal cats of β-tetra (2–4 mg), first reported by Barger & Dale (1910), was confirmed in two experiments. Activity was much reduced in three reserpine-treated spinal cats; 15 min after infusion of noradrenaline (50 μg/kg/min) responses to injections of tyramine and of β-tetra (1–2 mg/kg) were still less than in untreated animals. At that time the blood pressure was low and steady.

Rats. β-Tetra had less pressor effect in reserpine-treated pithed rats than in untreated rats. Table 1 shows the results of experiments in which β-tetra (80 μg) was injected before and after infusions of noradrenaline. After the infusion of noradrenaline the pressor response to β-tetra was larger than before. Fig. 3 shows a record of blood pressure of a reserpine-treated pithed rat and illustrates the increase in response 15 min after a noradrenaline infusion.

ACTIONS OF β-TETRA AFTER ADRENALECTOMY AND GANGLION BLOCKADE IN RATS

Three rats were adrenalectomized two weeks before use and were then pithed. No reduction in the pressor activity of β-tetra relative to that of

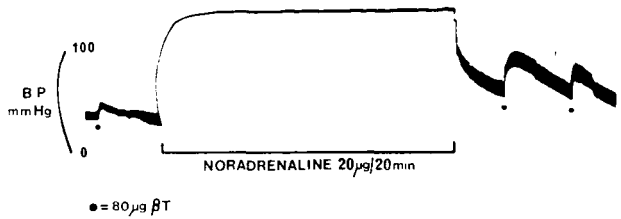

FIG. 3. Record of blood pressure from pithed rat which had received reserpine (2 doses of 2·5 mg/kg on each of two days before use, given intraperitoneally). β-Tetra (80 μg) had little pressor action. Noradrenaline (20 μg) infused during 20 min, caused a prolonged pressor response. Subsequent pressor responses to β-tetra were larger than before the infusion.

TABLE 1. THE PRESSOR RESPONSES TO β-TETRA IN RESERPINE-TREATED PITHED RATS MEASURED BEFORE AND AFTER INFUSION OF NORADRENALINE

Dose of β-tetra μg	Amount of noradrenaline infused μg	Pressor response before infusion mm Hg	Pressor response after infusion mm Hg	Ratio of pressor response after infusion to pressor response beforehand
80	20	10	45	4·5 : 1
80	10	12	29	2·2 : 1
80	10	10	15	1·5 : 1
80	20	8	27	3·4 : 1
60	20	7	15	2·1 : 1
60	—	17	—	—

Infusions of noradrenaline were given over 10 or 20 min period at the rate of 1 μg/min/rat.

tyramine was seen. In a fourth rat, acute adrenalectomy did not modify blood pressure responses to β-tetra and tyramine.

In other experiments, the action of hexamethonium on the blood pressure response to β-tetra was examined. There was only slight inhibition of the response to β-tetra, but complete block of the response to nicotine used at an initially equipressor dose.

Discussion

The potent pressor action of β-tetra in anaesthetized and spinal cats has been confirmed; this effect also occurs in the pithed rat. Substitution of one amine hydrogen atom by alkyl groups of increasing chain length alters activity. Methyl-β-tetra has less pressor activity in both cats and rats. Larger alkyl groups are depressor in the anaesthetized cat and much less potent than β-tetra as pressor agents in the pithed rat. Adrenaline-blocking potency and potency in producing depression of respiration were progressively reduced by the introduction of methyl, ethyl and propyl groups, but were again increased slightly when the substituent chain length was increased to four carbon atoms (butyl-β-tetra).

The tachyphylaxis to the pressor actions of β-tetra observed with cats has previously been noted by Barger & Dale (1910) and by Cloetta & Waser (1913) in dogs. Cross-tachyphylaxis between the β-tetra derivatives was also reported by the latter authors. Ethyl β-tetra, as found previously, had much less pressor action than either of the lower homologues. Respiratory depression following injection of β-tetra, methyl-β-tetra or ethyl-β-tetra as observed by Cloetta & Waser was also confirmed. Bovet & others (1952), on the other hand, did not mention the effects of the drug upon respiration.

Adrenaline blocking potency did not increase with increasing *N*-alkyl chain length. In contrast, Bovet & others (1952), who used dogs, reported that ethyl-β-tetra was more potent in blocking the pressor action of adrenaline than either the unsubstituted or the methyl derivative. In the present experiments with cats, the duration of adrenaline blockade produced by ethyl-β-tetra was longer lasting than the blockade produced by the compounds of lower molecular weight, but its adrenaline blocking potency was slightly less.

Reserpine treatment, but neither adrenalectomy nor effective ganglion-blocking doses of hexamethonium, reduced the pressor effect of β-tetra. These findings suggest that direct release of noradrenaline from sympathetic nerve endings may be a significant component of the drug's pressor action. Such an effect could explain the findings of Bacq (1936) that β-tetra failed to cause contraction of the denervated or cocaine-treated nictitating membrane in the cat, although there was contraction of the normal innervated membrane.

The failure of noradrenaline infusions to restore pressor responses to β-tetra in resperpine-treated cats is reminiscent of the findings of Burn & Rand (1958) with amphetamine in reserpinized cats. They were unable to obtain restoration of the pressor response to amphetamine if an

injection of amphetamine had been given before the infusion. Rand (personal communication) has pointed out that this is true for other amines which, like amphetamine and β-tetra, often produce tachyphylaxis. In the pithed rat, tachyphylaxis to the pressor action of β-tetra was not seen, and pressor responses to β-tetra were readily restored by noradrenaline infusions in reserpine-treated preparations. It may be that an anti-sympathomimetic acition of β-tetra, manifest in the present experiments as an antagonism towards the pressor action of adrenaline, might at least partly account for the tachyphylaxis occurring in normal cats, as well as for the failure of noradrenaline to "restore" the pressor action of β-tetra in reserpine-treated cats.

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References

Bacq, Z. M. (1936). *Mém. Acad. r. Méd. Belg.*, **25**, 1–61.
Bamberger, E. & Müller, R. (1888). *Ber dt. chem. Ges.*, **21**, 1112–1125.
Barger, G. & Dale, H. H. (1910). *J. Physiol., Lond.*, **41**, 19–59.
Bovet, D. (1959). Nobel lecture, presented 11th Dec., 1957, reproduced in *Science, N.Y.*, **129**, 1255–1264.
Bovet, D., Bovet-Nitti, F. & Longo, V. G. (1952). *Rc. 1st. sup. Sanita*, **15**, 925–952.
Bovet, D., Bovet-Nitti, F., Sollero, L. & Marini-Bettolo (1951). *Experientia*, **7**, 232–234.
Bovet, D., Sollero, L & Marotta, M. (1952). *Rc. 1st. sup. Sanita*, **15**, 905–924.
Bovet, D. & Virno, M. (1952). *Ibid.*, **15**, 870–904.
Burn, J. H. (1952). *Practical Pharmacology*, pp. 47–48. Oxford: Blackwell Scientific Publications.
Burn, J. H. & Rand, M. J. (1958). *J. Physiol., Lond.*, **144**, 314–336.
Cloetta, M. & Waser, E. (1913). *Arch. exp. Path. Pharmak.*, **98**, 398–435.
Craig, J. C., Moore, B. & Ritchie, E. (1959). *Aust. J. Chem.*, **12**, 447–457.
Gaddum, J. H. (1941). *J. Physiol., Lond.*, **99**, 257–264.
Pennefather, J. N. & Rand, M. J. (1960). *Ibid.*, **154**, 277–287.
Shipley, R. E. & Tilden, J. J. (1947). *Proc. Soc. exp. Biol. Med.*, **64**, 453–456.