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EFFECT OF NICOTINE, NORNICOTINE AND ALLYLNORNICOTINE ON THE DIURETIC RESPONSE TO WATER IN RATS

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The LD50 in mice for nicotine, (−)-nornicotine and allylnornicotine given intraperitoneally was respectively 10 mg/kg, 18.8 mg/kg and 93.3 mg/kg. Whilst nicotine inhibited the renal response in rats to water, (−)-nornicotine and allylnornicotine were without effect. Nicotine antidiuresis was not antagonized by (−)-nornicotine or by allylnornicotine.

Nicotine is known to inhibit the diuretic response to water, an action mediated through the hypothalamic-neurohypophysial system (Burn, Truelove & Burn, 1945; Bisset & Walker, 1957). This action is not blocked by ganglion blocking agents such as pentamethonium and hexamethonium or by atropine or atropine-like compounds (Supek & Eisen, 1953; Bisset & Walker, 1957; Schnieden, 1960). It therefore seemed of interest to see if some compounds related to nicotine (1-methyl-2-pyrid-3′-ylpyrrolidine) also produced antidiuresis and also if these related compounds could antagonize the antidiuretic effect of nicotine. The compounds investigated were (−)-nornicotine ((−)-2-pyrid-3′-ylpyrrolidine) and allylnornicotine (1-allyl-2-pyrid-3′-ylpyrrolidine).

METHODS

Adult albino male rats weighing approximately 200 g were used. The effect of the drugs on the diuretic response to water was tested on groups of 8 animals (Schnieden, 1960). Initially the animals in the groups were randomly allocated to one of the drug treatments and cross-over experiments were then carried out at weekly intervals until all animals in the group had received all treatments. All drugs were given subcutaneously 45 min after the second dose of water was administered. The water load remaining at that time was considered the initial water load. For the next 90 min urine volumes were noted at 30-min intervals. Results were expressed as % of the initial water load excreted during this 90-min period. The following drugs were injected subcutaneously: nicotine hydrogen tartrate 7.5 mg/kg; (−)-nornicotine either 3.75 mg/kg or 10 mg/kg; allylnornicotine 20 mg/kg. Control groups received corresponding injections of 0.9% sodium chloride solution. In addition the above drugs were injected in increasing dosage intraperitoneally into groups of mice (10 mice per dose) in order to determine their LD50. The (−)-nornicotine was obtained from Fluka A.G.

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(Switzerland) and the allyl derivative was prepared according to von Braun & Weissbach (1930) giving after fractionation a yield of approximately 20% of allylnornicotine, b.p. 150°/30 mm.n $\frac{25^\circ}{D}$ 1.526.

The infra-red film spectrum of the allyl compound was compared with that of (−)-nornicotine and the presence of the allyl group confirmed by various bands, e.g., at 1,640 cm.$^{-1}$ (w), (C=C) and 920 cm.$^{-1}$ (s), (=CH_2).

RESULTS

The LD50 in mice of nicotine, (−)-nornicotine and allylnornicotine was respectively 10 mg/kg, 18.8 mg/kg and 93.3 mg/kg. The LD50 for nicotine is calculated for nicotine base from the results obtained with nicotine hydrogen tartrate.

In rats nicotine hydrogen tartrate (7.5 mg/kg) significantly inhibited the diuretic response to water (Table 1). However, (−)-nornicotine and allylnornicotine in doses

TABLE 1

EFFECT OF NICOTINE, (−)-NORNICOTINE, AND ALLYLNORNICOTINE ON THE DIURETIC RESPONSE TO WATER

Values represent % of initial water load excreted during the 90-min period after injection of the drugs (mean±s.e. for 8 animals)

Saline	Nicotine hydrogen tartrate 7.5 mg/kg	(−)-Nornicotine 3.75 mg/kg	Allyl-nornicotine 20 mg/kg
77·1±9·8	39·5±8·8	87·7±8·4	54·0±13·5

of 3.75 mg/kg and 20 mg/kg respectively failed to inhibit this response, e.g., comparing the control response with the response to allylnornicotine $t=1.4$ $P>0.1$. In a similar series of experiments, (−)-nornicotine (10 mg/kg) caused no inhibition in diuretic response; controls 95.3±14.1 (mean±s.e. 8 animals), (−)-nornicotine 106.7±8.9 (8 animals) $t=0.7$, $P>0.4$.

Nicotine antidiuresis in the rat was not antagonized by the subcutaneous injection of (−)-nornicotine (10 mg/kg) given at the same time as the nicotine. The % water load excreted following injections of nicotine plus 0.9% sodium chloride solution was 43.4±3.0, whilst following injections of nicotine plus l-nornicotine it was 52.0±6.0 $t=1.4$, $P>0.1$ (mean±s.e. for 8 animals). Similarly combination of nicotine (7.5 mg/kg body weight) with allylnornicotine (20 mg/kg) did not reduce the antidiuretic action of nicotine but in fact enhanced it. The % water load excreted following injections of nicotine and equivalent volume of 0.9% sodium chloride solution was 40.7±3.5, whilst following injections of nicotine and allylnornicotine it was 24.1±5.0 $t=2.8$, $P<0.02$. It was noticeable that some of the animals treated with nicotine and allylnornicotine had convulsions for a few minutes following injections of the two drugs.

DISCUSSION

Hicks & Sinclair (1947) have reported that (−)-nornicotine is as toxic as nicotine in the rat. However, Larsen, Haag & Finnegan (1945) noted that (−)-nornicotine intraperitoneally in mice had an LD50 of 21.7 mg/kg whilst nicotine had an LD50 of 10.3 mg/kg. These latter values agree closely with those obtained in the present investigation.

Nicotine produces its antidiuretic effect by stimulating neurohypophysial secretion. The failure of (−)-nornicotine to produce antidiuresis in doses up to half its LD50 could be due to failure of the drug to reach the central nervous system. This is unlikely, as, in mice, death is preceded by convulsions similar to those caused by nicotine. Hicks, Mackay & Sinclair (1947) have shown that (−)-nornicotine is much less potent than nicotine in stimulating the cervical sympathetic ganglion in the cat. If this marked difference in potency similarly applies to stimulation of synapses in the supra-optic nucleus of the rat, then the failure of (−)-nornicotine to produce antidiuresis could be explained. Allylnornicotine can also cause nicotine-like convulsions and hence presumably also reaches the central nervous system. Whether like (−)-nornicotine it is less potent than nicotine in stimulating the cervical sympathetic ganglion has yet to be determined.

Morphine antidiuresis can be antagonized by nalorphine, its *N*-allyl derivative (Winter, Gaffney & Flataker, 1954 ; Schnieden & Blackmore, 1955). The latter drug probably acts as a competitive antagonist. Nicotine antidiuresis, however, was not antagonized by (−)-nornicotine nor by allylnornicotine.

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