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SOME PHARMACOLOGICAL ACTIONS OF PIPERIDINE, PYRROLIDINE, AND OF PRESSOR CONCENTRATES FROM DOG URINE

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Euler isolated piperidine from urine in 1944, and in 1945 (a and b) described its actions on blood pressure, respiration, rabbit's intestine, and the motility of the unanaesthetized frog. He indicated the general similarity of its action to that of nicotine. The pharmacological activity of the pyrrolidines has not been fully investigated. Tunnicliffe and Rosenheim (1902) reported that N-methylpyrrolidine (25 mg. i.v.) produced an initial fall of the cat's blood pressure followed by a rise, and that the response was not abolished by section of the vagi.

Lockett (1944, 1946) described the preparation of pressor concentrates from both normal dog and normal human urine, and referred to these as base B concentrates. After the incomplete oxidation of these concentrates with potassium permanganate, the following substances can be identified in pharmacologically significant amounts: piperidine, pyrrolidine, dimethylamine, and ammonia. Chemical evidence showing that these four bases were absent in the original concentrates, though they could be obtained as degradation products from base B concentrates, is to be presented elsewhere. The present communication is concerned with the equally important problem of comparing the pharmacological action of base B concentrates with that of the suspected degradation products. This is particularly of interest since the actions of pyrrolidine have been relatively little studied.

METHODS

Chemical methods

Preparation of base B concentrates.—The dog urine used for these experiments was brought to *p*H 11.0, and was submitted to continuous ether extraction for 24–48 hours in order to remove piperidine (Euler, 1945), nicotine compounds (Lockett, 1944), *iso*-amylamine (Bain, 1914), and other ether soluble material. The urine was then distilled in steam from highly alkaline solution, and the distillate concentrated *in vacuo* at a low temperature, without the addition of acid, as previously described (Lockett, 1946). That this procedure eliminated any piperidine or pyrrolidine which might initially have been present in the urine was shown by the disappearance of either base deliberately added to the urine in a concentration of 0.2 per cent.

Pyrrolidine was synthesized from trimethylene glycol: trimethylene dibromide was converted to the 3-bromopropylphenyl ether (v. Braun and Beschke, 1906) which was condensed with KCN. The nitrile was reduced with Na in alcohol and the phenoxy group replaced by iodine with hydriodic acid; the pyrrolidine was distilled from alkaline solution and converted into the picrate, m.p. 112° C. (Found: C, 40.2; H, 4.28; N, 18.5. Calc. for $C_4H_9N.C_6H_3O_7N_3$: C, 40.0; H, 4.0; N, 18.67 per cent.)

Piperidine was purified as the picrate by recrystallization. For the preparation of the hydrochloride the base was liberated from the purified picrate.

Dibenamine (N-N-dibenzyl-β-chloroethylamine) was obtained in solution in propylene glycol (50 mg./c.c.) by courtesy of Dr. A. Wilson.

Pharmacological methods

The techniques employed for the pressor test on cats under chloralose, for acute sympathectomy, adrenalectomy, and evisceration have been described (Lockett, 1946).

Collection of blood from adrenal veins.—The animal was prepared for blood pressure records and

for intravenous injections. Forelimb veins were exposed, and a midline abdominal incision was made; loose ligatures were placed in position. After 30 min. heparin was administered to the animal, and one or both adrenal veins were cannulated. The fine valve tubing which extended from the cannula led through a puncture incision in the abdominal wall, and returned the blood to a cannulated opposite forelimb vein. A very small glass T-piece interpolated into the tubing close to the abdominal wall was used for the collection of blood samples. The lumbar vein was tied as it approached the adrenal gland, and the abdomen was closed. The dead space from the cannula tip to the arm of the T-piece varied from 0.4 to 0.65 c.c.

Perfusion of the superior cervical ganglion.—The technique of dissection and the nature of the perfusion fluid followed the detailed description given by Feldberg and Gaddum (1934). The slightly pulsatile perfusion pressure varied from 125 to 130 mm. Hg, and the outflow was 0.7 to 0.9 c.c./min. The eserine concentration used in the perfusion fluid was 1:10,000. The effluent fluid was tested on the frog's rectus abdominis.

Survival sympathectomy.—Dogs were used. The sympathetic chains were removed from the stellate ganglia to the pelvis, in a 3-stage operation under cyclopropane, by a technique not greatly different from that described by Cannon *et al.* (1929). Sympathectomy was completed in 4–6 weeks. The tracings shown and the results quoted were obtained by aseptic cannulation of anastomotic branches of either femoral or brachial arteries, 3–7 weeks after the completion of sympathectomy.

RESULTS

Six base B concentrates have been compared with solutions of piperidine and pyrrolidine in their actions on the blood pressure. Each concentrate was derived from 12 to 18 l. of dog urine, concentrated many hundredfold.

The relative activities of piperidine, pyrrolidine, and base B concentrates

In a series of 43 cats, under chloralose anaesthesia, and with mean carotid blood pressures between 110 and 130 mm. Hg, the sensitivity to both piperidine and pyrrolidine was found to vary greatly; the relative activity of pyrrolidine to piperidine, expressed in terms of base, varied from 2:1 to 0.6:1, pyrrolidine usually being slightly the more active. The intravenous injection of 1.5 mg. of either base into cats weighing from 2 to 4 kg. usually produced rises of blood pressure of 50 mm. Hg or more.

Since base B was examined in solution no comparison of activity could be made by weight. Piperidine and pyrrolidine are secondary amines and therefore give a red colour with β-naphthoquinone-4-sulphonic acid, a colour test which Euler (1945) used for the estimation of piperidine derived from normal urine. The pressor activity of three base B concentrates was too great to be explained in terms of their content of secondary amine, interpreted as piperidine and pyrrolidine, and determined colorimetrically, unless impurities were in part masking the colour reaction.

Whenever opportunity offered a comparison was made of the spontaneous alterations in the sensitivity of cats under chloralose anaesthesia to the intravenous injection of piperidine, pyrrolidine, base B concentrates, and adrenaline. In four cats in which sensitivity to adrenaline was unaltered or gradually increased in the course of two or three hours, sensitivity to pyrrolidine decreased greatly (e.g., 1:4); the sensitivity to piperidine also decreased (e.g., 1:2 or 2.5), whereas the response to base B concentrates was almost unaltered. Such a finding could only indicate that the pressor activity of base B concentrates was not due to their piperidine or pyrrolidine content: whatever the factors which contributed to such alterations in sensitivity, identical compounds should have been similarly affected.

Under rather deep chloralose anaesthesia, tachyphylaxis to pyrrolidine has frequently been observed in cats (Fig. 1), but it was not a constant finding. Such tachyphylaxis has not been demonstrated with piperidine or with base B concentrates.

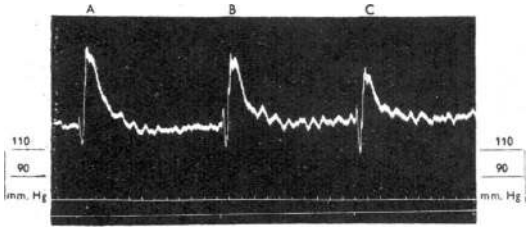

FIG. 1.—The tracings show the changes in the arterial blood pressure of a cat under chloralose anaesthesia following the injection of 5 mg. of pyrrolidine picrate (A), (B), and (C), at intervals of 5 min. Tachyphylaxis is seen. Time marker, 30 sec.

The influence of blocking agents

Interesting differences in the actions of piperidine, pyrrolidine, and base B concentrates were revealed after the use of autonomic blocking agents.

Tetraethylammonium chloride, given intravenously in a small dose (e.g., 10 mg./kg.) to six cats under chloralose anaesthesia, reduced, abolished, or reversed the pressor responses to piperidine and pyrrolidine, and caused only moderate reduction

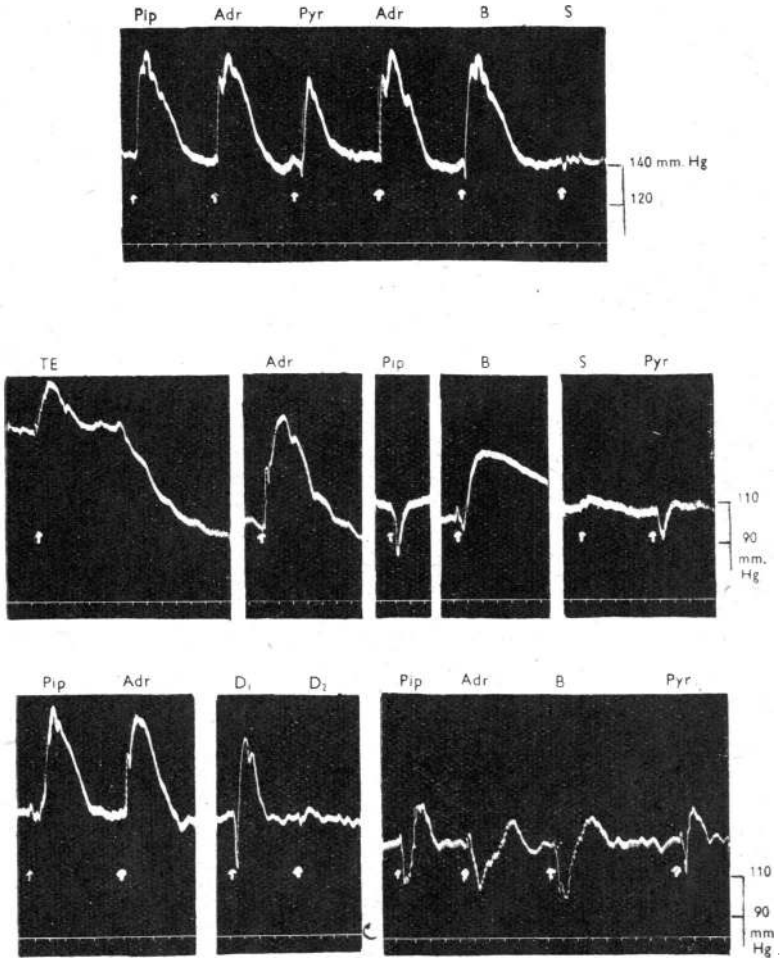

FIG. 2.—Cat, 2.7 kg., chloralose. Arterial blood pressure records; all injections intravenous. Top and middle records: Pip = 1.5 mg. piperidine HCl/8 c.c. Adr = 1.5 μg. adrenaline HCl/8 c.c. Pyr = 5 mg. pyrrolidine picrate/8 c.c. B = base B concentrate, 8 c.c. S = 8 c.c. normal saline. TE = 30 mg. tetraethylammonium chloride/10 c.c. saline. Pause of 10 min. made here. Bottom record: One hour after TE, when the effect of tetraethylammonium chloride had completely disappeared and the base line was restored to normal, the sensitivity of the cat to the compounds was unchanged; compare Pip and Adr with the first two injections of the top record. D_1 = 40 mg. dibenamine/0.8 c.c. propylene glycol, diluted to 10 c.c. with saline. D_2 = 0.8 c.c. propylene glycol similarly diluted. Note depressor responses after dibenamine.

in responses to base B concentrates (Fig. 2). Larger doses of tetraethylammonium chloride (e.g., 20 and 30 mg./kg.) reversed the responses to piperidine and pyrrolidine, whereas they never reversed but only reduced the response to base B concentrate.

Dibenamine was given intravenously, well diluted with saline, to 5 dogs under phenobarbitone anaesthesia and to 6 cats under chloralose anaesthesia, in doses varying from 5 to 20 mg./kg. Dibenamine was itself pressor. It reversed the responses to adrenaline more readily than those to piperidine or base B concentrates; the response to pyrrolidine was usually the least affected (Fig. 2). Reversed responses after dibenamine were not abolished by atropine sulphate (1 mg./kg.). The effect of dibenamine on the tachycardia produced after atropine in chloralosed cats by equipressor doses of piperidine, pyrrolidine, and adrenaline was, in the three experiments, a very similar percentage reduction of the maximum heart rate.

The effects of acute total sympathectomy

In cats under chloralose anaesthesia sympathectomy reduced the pressor response to piperidine and to pyrrolidine, whereas the pressor responses to base B concentrates and to adrenaline were little or not at all reduced. On two such occasions, despite the lowered base line after acute sympathectomy, almost as high a maximum value of the blood pressure was reached after as before sympathectomy. Evisceration reduced the responses to all three compounds.

The significance of the suprarenal glands

The sympathetic innervation of the suprarenal glands is composed of preganglionic fibres. Drugs which stimulate ganglion cells may therefore be expected to act directly on the medulla of these glands. In 3 cats under chloralose anaesthesia, a careful section of all nerve fibres at their points

of entry into the adrenal glands reduced the pressor responses to piperidine and pyrrolidine. These were not further reduced by subsequent adrenalectomy (Fig. 3). Such a finding was both contrary to expectation and to all the other evidence obtained, which had supported the view that these drugs have a stimulant action on ganglion cells.

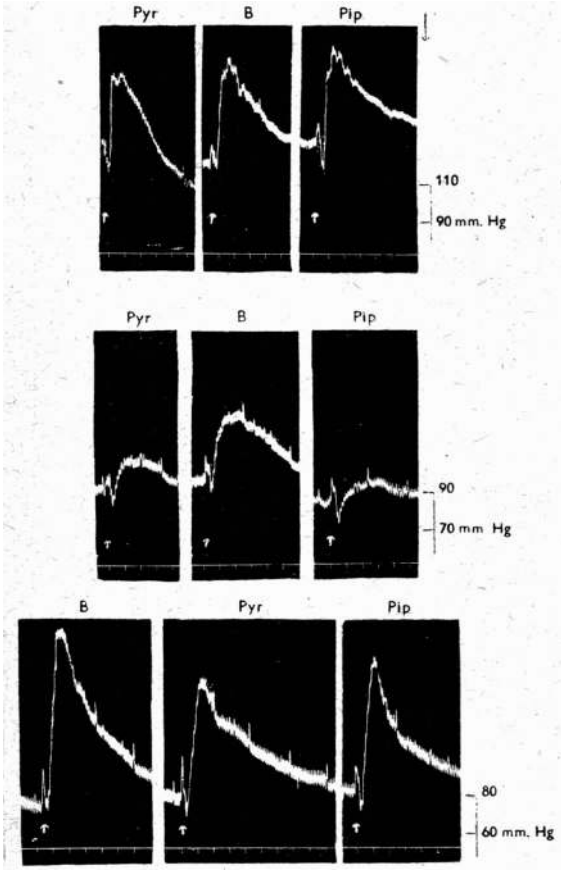

FIG. 3.—Cat, 2.7 kg., chloralose. Arterial blood pressure records. Top and middle records: Pyr = 4 mg. pyrrolidine picrate. B = 4 c.c. base B concentrate. Pip = 6 mg. piperidine picrate. Bilateral adrenalectomy at arrow. Bottom record: B = 6 c.c. base B concentrate. Pyr = 8 mg. pyrrolidine picrate. Pip = 12 mg. piperidine picrate. Time marker, 30 sec.

Two further experiments were carried out. Simple section of the splanchnic nerves did not alter the pressor responses which followed the intravenous injection of piperidine and pyrrolidine, but these responses were reduced by subsequent adrenalectomy. Paralysis of synaptic action by the intravenous injection of 40 mg. of nicotine, intravenously, in divided doses, into spinal cats, abolished the pressor responses to 4 mg. each of the bases, piperidine, pyrrolidine, and nicotine; the response to adrenaline remained. The results of these last two experiments conform with expectation: those of the previous experiment remain unexplained.

It was shown in two series of experiments that piperidine and pyrrolidine produce part of their pressor action by the liberation of adrenaline or another pressor compound from the adrenal glands.

In the first, blood was collected simultaneously from the femoral and adrenal veins, both before and during pressor responses. The blood samples were injected intravenously into another similar animal whose blood pressure was being simultaneously recorded. Six dogs and eight cats were used. Large pressor responses to piperidine and pyrrolidine were accompanied by the liberation of a pressor compound into the venous blood of a single adrenal gland which equated with 5 or 7 μg. of *dl*-adrenaline. The control adrenal and femoral blood samples were without pressor activity. Base B concentrates differed from piperidine and pyrrolidine; the adrenal venous blood collected during large pressor responses to base B concentrates was without pressor action on the blood pressure (Fig. 4). The quantities of adrenaline which appeared to be liberated from the adrenal glands during pressor responses to piperidine and pyrrolidine can be detected by chemical means.

In a second series of experiments, carried out on six cats under chloralose, samples of control adrenal vein blood and adrenal venous blood collected during pressor responses to piperidine and pyrrolidine were examined colorimetrically (Shaw, 1938). In two of the six experiments a well-marked blue colour was given by the control blood samples, indicating the continuous excretion of reducing compound; in the other four experiments the control blood yielded practically no colour. In all six experiments, a large increase in the reducing compound estimated in the adrenal venous blood occurred during the pressor responses to piperidine and pyrrolidine; piperidine usually caused the liberation of 1.5 to 1.3 times as much reducing compound as did pyrrolidine in equipressor doses. It should be stated that the amounts of reducing compound, estimated chemically as adrenaline, which were liberated from the adrenal glands by piperidine and pyrrolidine were, in all experiments, substantially less than half (e.g., 25–34 per cent) those which would account for the pressor responses obtained when such blood was

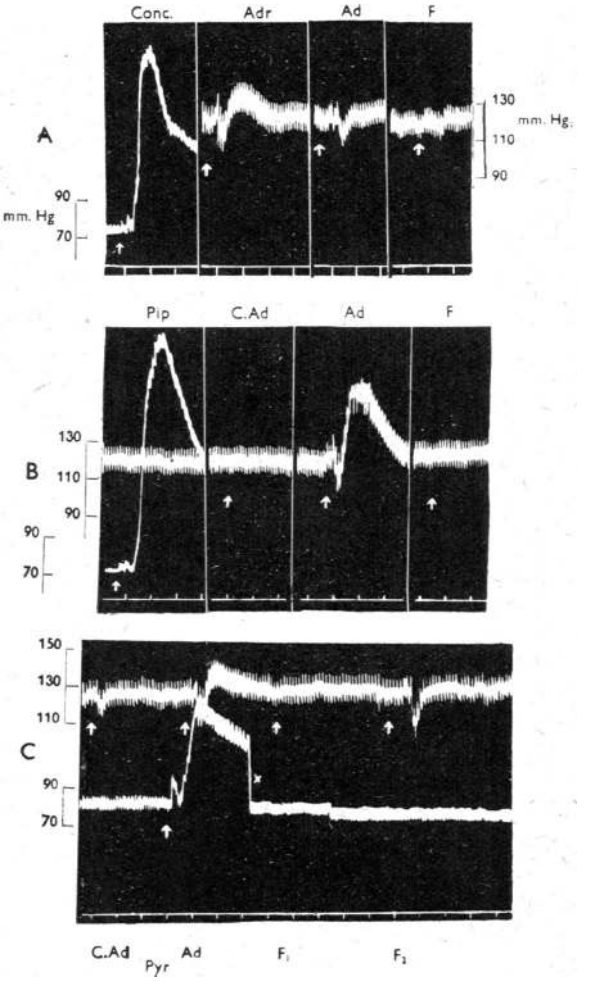

FIG. 4.—All but the first tracing in A and the upper tracings in B and C are records of the femoral blood pressure of dog 1, 7.6 kg., prepared for injections by femoral venous cannula; the other tracings are records of the femoral arterial pressure of dog 2, 8 kg., prepared by cannulation of both femoral and one adrenal vein for intravenous injections and the collection of femoral and adrenal venous blood samples.

A. Conc. = 20 c.c. base B concentrate to dog 2; during the response, blood was collected simultaneously from the femoral and adrenal veins. F = 5 c.c. of this femoral blood, and Ad = 3 c.c. of this venous blood injected into dog 1 without effect on the blood pressure. Adr = 5 μg. of adrenaline to dog 1.

B. Pip = 15 mg. piperidine HCl to dog 2. Whereas C.Ad = 4.0 c.c. control adrenal blood and F = 3.5 c.c. of femoral venous blood collected from dog 2 during the piperidine response (Pip) were without pressor effect, Ad = 3.5 c.c. of adrenal venous blood collected during the piperidine response had pressor action when injected into dog. 1.

C. The record shows the same procedure repeated with positive effect when dog 2 received 15 mg. pyrrolidine picrate (Pyr); C.Ad = 3 c.c. control adrenal blood; Ad = 3 c.c. adrenal and F_1 = 3 c.c., F_2 = 5 c.c. of femoral blood, all collected from dog 2 during the pyrrolidine response, and injected into dog 1. Time marker throughout 30 sec.

injected into another animal and was equated with *dl*-adrenaline.

Action in recovered sympathectomized dogs

The sympathetic chains of two dogs were removed from the stellate ganglia in the chest down to the pelvis, and after an interval of three weeks to allow time for the degeneration of the postganglionic fibres, the actions of piperidine and pyrrolidine were observed in eight experiments. Pyrrolidine and piperidine were found to have a depressant action on the blood pressure. Fig. 5 shows the responses of one such dog to 15 mg. pyrrolidine picrate and 10 mg. piperidine hydrochloride before and after survival sympathectomy. Tetraethylammonium bromide, when injected intravenously into two such preparations, failed to produce the customary fall in blood pressure which was certainly to be seen in one of these dogs before survival sympathectomy. Tetraethylammonium bromide did not abolish the depressor responses given in these preparations to piperidine and pyrrolidine, but 2 mg. atropine sulphate given intravenously reduced, and a further 2 mg. atropine sulphate abolished, the depressor reactions.

Cocaine, which prior to sympathectomy had not altered the pyrrolidine responses, and had slightly increased the piperidine responses, did not significantly increase the reversed responses to these two compounds encountered after sympathectomy (Fig. 6), which were also unaffected by dibenamine. Attempts to obliterate the action of dibenamine in these dogs by the use of sodium thiosulphate (Nomaguchi and Goodman, 1946)

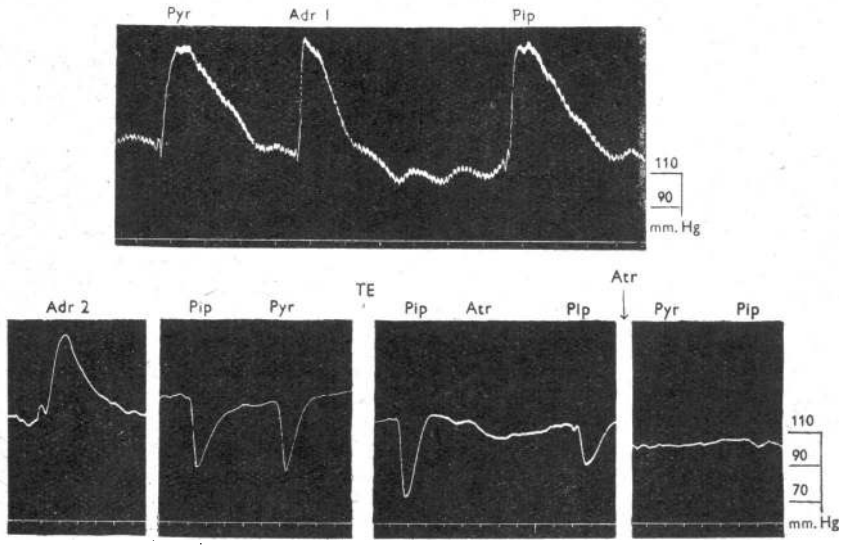

FIG. 5.—The tracings were taken under aseptic conditions from an anastomotic branch of the R. femoral artery of a dog, 7.5–7.7 kg., under phenobarbitone anaesthesia. The upper tracings were obtained before survival sympathectomy, and the lower were made five weeks after the completion of the last operative stage. Injections were given intravenously. Pyr = 15 mg. pyrrolidine picrate; Pip = 10 mg. piperidine HCl; Adr 1 = 20 μg. adrenaline chloride; Adr 2 = 4 μg. adrenaline chloride; Atr = 2 mg. atropine sulphate; TE = 100 mg. tetraethylammonium bromide in 20 c.c. normal saline. Time marker, 30 sec.

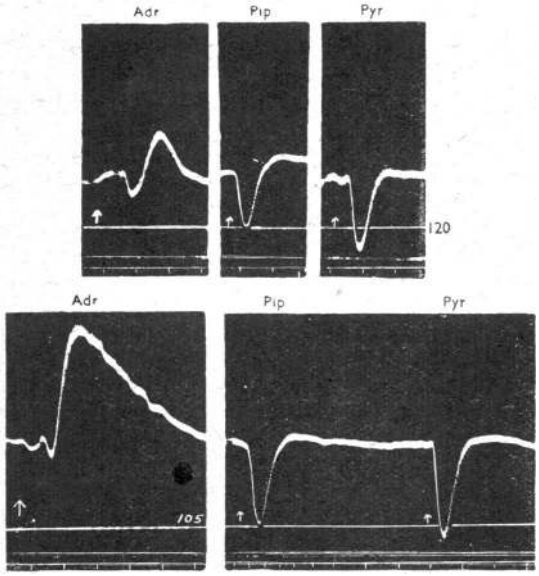

FIG. 6.—Dog, 7.6 kg., phenobarbitone. Record of the arterial blood pressure taken aseptically from a branch of the L. femoral artery, 19 days after the completion of survival sympathectomy. Intravenous injections: Adr = 2 μg. adrenaline HCl; Pip = 10 mg. piperidine HCl; Pyr = 15 mg. pyrrolidine picrate. Between the upper and lower tracings 30 mg. of cocaine HCl were given subcutaneously, and 40 min. were allowed to elapse. Time marker, 30 sec.

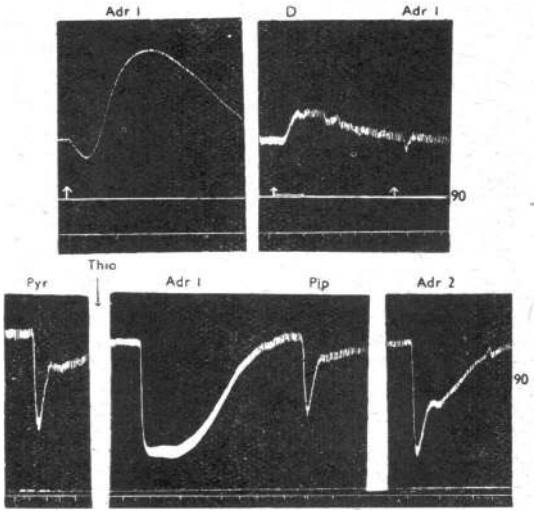

FIG. 7.—Dog, 7.7 kg., phenobarbitone. Aseptic record of the arterial blood pressure 46 days after the completion of survival sympathectomy. Intravenous injections: Adr 1 = 7 μg. adrenaline tartrate; D = 50 mg. dibenamine; Pyr = 15 mg. pyrrolidine picrate; Pip = 10 mg. piperidine HCl; Adr 2 = 2 μg. adrenaline acid tartrate. At arrow 20 c.c. of 10 per cent sodium thiosulphate injected slowly. Time marker, 30 sec.

resulted in a great potentiation of the adrenaline reversals, whilst the reversed responses to piperidine and pyrrolidine remained unaffected (Fig. 7).

Action on respiration

Euler (1945) described the stimulant action of piperidine on the respiration. The effect of piperidine, pyrrolidine, and base B concentrates on the respiration, when administered in equipressor doses, was studied in 5 cats under chloralose anaesthesia. Fig. 8 shows the great similarity of the respiratory changes after the intravenous injection of equipressor doses of piperidine and pyrrolidine; base B concentrate in an equipressor dose also stimulated respiration, but the effect was less dramatic and lasted longer (Fig. 8).

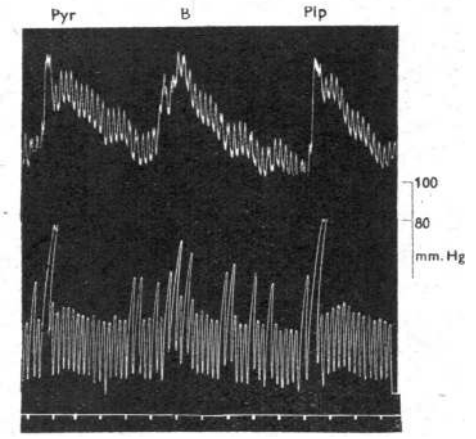

FIG. 8.—Cat, 3.2 kg., chloralose. The upper tracings are a record of the arterial blood pressure, the lower a simultaneous record of respiration. Intravenous injections: Pyr = 1 mg. pyrrolidine picrate; B = 3 c.c. base B concentrate; Pip = 0.75 mg. piperidine HCl. Time marker, 30 sec.

Action on sympathetic ganglia

It was found that although piperidine and pyrrolidine did stimulate the liberation of acetylcholine from the perfused superior cervical ganglion of the cat under chloralose, the dose required to produce this effect was very large in comparison with that which produced a considerable rise of blood pressure in the whole animal. Fig. 9 shows the responses of the arterial blood pressure of such a cat to the intravenous injection of 7 mg. pyrrolidine picrate, 5 mg. piperidine hydrochloride, and 2 c.c. base B concentrate (upper tracing). The lower tracing shows that approximately 1/10 of these pressor doses of piperidine and pyrrolidine when injected into the arterial cannula supplying the perfused cervical ganglion

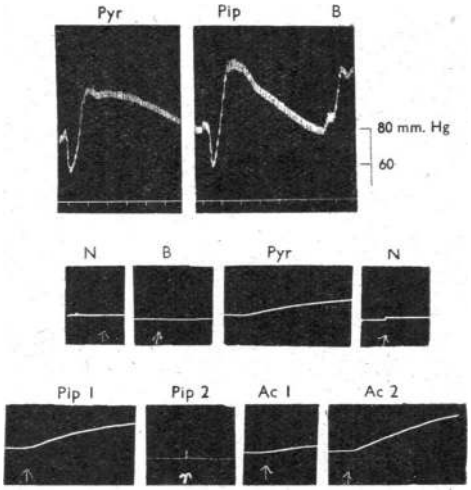

FIG. 9.—Upper tracing. Cat, 2.7 kg., chloralose. The record is of the arterial blood pressure; injections were intravenous. Pyr = 7 mg. pyrrolidine picrate; Pip = 5 mg. piperidine HCl; B = 2 c.c. base B concentrate. The R. superior cervical ganglion of this cat was being separately perfused; the perfusate contained 1 in 10,000 eserine.

Lower tracings show the responses of the eserinized frog rectus to 1.5 c.c. of the effluent perfusate, diluted 1 to 1.4; N = normal effluent; and after the following injections had been made into the S.C.G. cannula: B = 0.75 c.c. base B concentrate; Pyr = 1 mg. pyrrolidine picrate in 0.5 c.c.; Pip = 0.5 mg. piperidine HCl in 0.5 c.c. The remaining rectus responses follow the direct injection into the 15 c.c. bath of Pip 2 = 1 mg. piperidine HCl; Ac 1 = 0.25 c.c. and Ac 2 = 0.6 c.c. of a 1 in 1,000,000 solution of acetylcholine.

preparation in the same animal caused the liberation of acetylcholine into the effluent perfusate. Neither 1/10 nor 1/3 the pressor dose of base B concentrate similarly injected caused liberation of acetylcholine.

Action on uterus and intestines

Euler found that 0.5 mg. piperidine hydrochloride stimulated the contractions of rabbit's intestine, and that the effect produced was very similar to that of nicotine and was not abolished by atropine.

In four experiments piperidine and pyrrolidine were found to produce submaximal contraction of the guinea-pig ileum in a concentration of 10^{-4}, and this effect was prevented by atropine sulphate in a concentration of 5×10^{-4}. In three experiments 3×10^{-4} piperidine caused a greater increase in tone in the horns of a guinea-pig uterus than pyrrolidine did in the same concentration; each drug abolished the spontaneous activity and

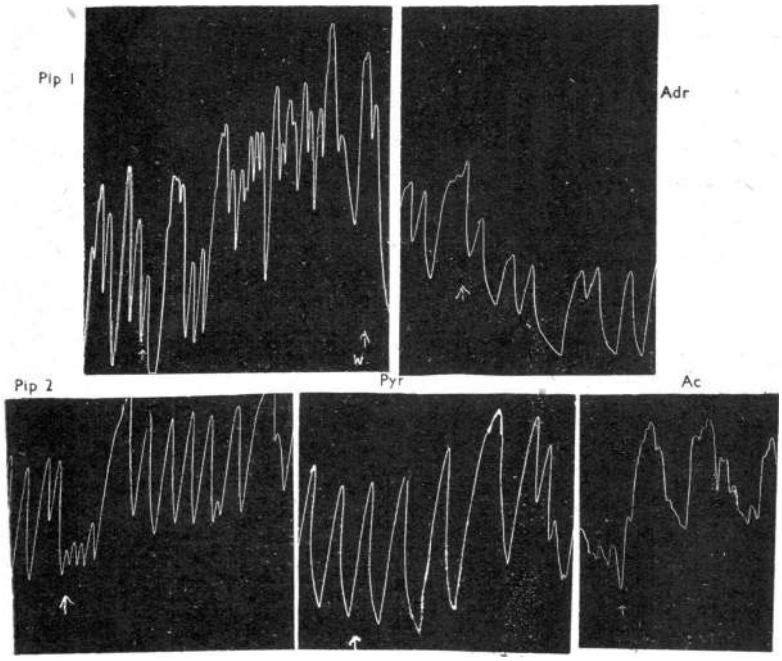

FIG. 10.—The record shows the responses of the non-pregnant cat uterus, suspended in oxygenated Tyrode solution, at 37° C., in a 20 c.c. bath, to the injection of the following solutions: Pip 1 = 1 mg. piperidine HCl; Adr = 10 μg. adrenaline chloride; Pip 2 = 0.5 mg. piperidine HCl; Pyr = 0.7 mg. pyrrolidine picrate; Ac = 0.5 mg. acetylcholine.

neither was effective in the presence of 5×10^{-4} atropine sulphate. (The concentrations given are those of the picrates.) In the non-pregnant cat uterus, whereas adrenaline caused inhibition, piperidine and pyrrolidine caused an increase in tone (Fig. 10), and were ineffective in the presence of atropine sulphate (5×10^{-4}).

Action on the nictitating membrane

Piperidine and pyrrolidine both caused contraction of the nictitating membrane in 4 cats and 2 dogs; the drugs were injected intravenously in doses sufficient to produce a rise in the mean arterial pressure of 40–60 mm. Hg.

DISCUSSION

Of the four basic degradation products obtained by partial oxidation of base B concentrates, piperidine and pyrrolidine exhibited pressor activity. The amounts of piperidine and pyrrolidine derived from base B concentrates have been approximately determined (Lockett, 1949) and might account for rather less than half the pressor action of the original base B concentrates, were it not for the dissimilarity in the actions of base B concentrates and these two bases. The main features of this dissimilarity are that the pressor action of base B concentrates is not reversed by tetraethylammonium chloride, and is only very slightly reduced after acute sympathectomy, denervation, or removal of the suprarenal glands. Piperidine and pyrrolidine cause the liberation of acetylcholine into the effluent perfusate from the superior cervical ganglion and of a pressor compound into the adrenal venous blood; base B concentrates do not, even when supramaximal pressor doses are employed.

These dissimilarities indicate that piperidine and pyrrolidine were not present as such in the original base B concentrates, although they can be obtained from base B concentrates by oxidative degradation, and that the pressor activity of these concentrates is due to some compound other than piperidine or pyrrolidine.

That piperidine and pyrrolidine have almost identical action is shown by the results recorded in this paper. Euler in 1945 described the action of piperidine as "synatropic," like that of nicotine, and commented on the absence of "muscarine effects." The presence of the latter in the action of piperidine and pyrrolidine has, however, been disclosed in experiments (i) on animals in which the postganglionic fibres of the sympathetic system have been allowed to degenerate, (ii) in perfusions of the superior cervical ganglion, (iii) on the non-pregnant cat uterus, and (iv) on the guinea-pig uterus and ileum.

SUMMARY

1. Piperidine and pyrrolidine have approximately equal pressor activity.

2. The pressor actions of piperidine and pyrrolidine were reversed by large doses of tetraethylammonium chloride, and by dibenamine, in cats and dogs (Fig. 2).

3. The pressor responses to piperidine and pyrrolidine were considerably reduced by acute total sympathectomy, and less markedly by removal of the adrenals or evisceration.

4. A pressor compound appeared in the adrenal venous blood during the pressor responses to piperidine and pyrrolidine (Fig. 4).

5. Pyrrolidine and piperidine produced depressor responses in dogs which had recovered from total sympathectomy. These responses were reduced by tetraethylammonium chloride, abolished by atropine, and unaffected by dibenamine and cocaine.

6. Pyrrolidine and piperidine stimulated respiration, caused contraction of the nictitating membrane and liberation of acetylcholine from the perfused cervical ganglion. Both compounds induced contraction of the guinea-pig ileum, increased the tone of the guinea-pig uterus and of the non-pregnant cat uterus ; these responses were antagonized by atropine.

7. The pharmacological actions of base B concentrates qualitatively resembled those of piperidine and pyrrolidine in that base B concentrates stimulated respiration and shortened the nictitating membrane. The pressor actions were reduced by dibenamine, by tetraethylammonium chloride in a dose of 10 mg./kg., and by evisceration.

8. The actions of base B concentrates differed from those of piperidine and pyrrolidine in that the pressor action of the former was not reversed by tetraethylammonium chloride 30 mg./kg., and that it was only very slightly reduced after acute sympathectomy, denervation, or removal of the suprarenal glands. No pressor compound appeared in the adrenal venous blood pressor responses to base B concentrates ; they also failed to liberate acetylcholine from the cat's superior cervical ganglion.

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