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Effect of Pentazocine on Pressor Responses of Epinephrine and Levarterenol

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Abstract □ In rats anesthetized with pentobarbital, pentazocine potentiated the pressor response of two exogenous amines, epinephrine and levarterenol. Although the mechanism for the pentazocine-induced potentiation of the pressor amines has not been proven, it is speculated that pentazocine may increase the blood pressure response of certain amines by interacting with the sympathetic nervous system.

Keyphrases □ Pentazocine—effect on pressor responses of epinephrine and levarterenol, rats □ Epinephrine—pressor responses, effect of pentazocine, rats □ Levarterenol—pressor responses, effect of pentazocine, rats □ Pressor responses—epinephrine and levarterenol, effect of pentazocine, rats □ Analgesics—pentazocine, effect on pressor responses of epinephrine and levarterenol, rats □ Adrenergic agents—epinephrine and levarterenol, pressor responses, effect of pentazocine, rats

Pentazocine, a weak narcotic antagonist of the benzomorphan series, was first synthesized by Archer *et al.* (1). It is an effective analgesic in humans (2) with a low incidence of adverse effects (3).

Whereas the cardiovascular effects of morphine are hypotension and bradycardia, pentazocine produces a rise in systemic arterial blood pressure and heart rate (2). Therefore, Hobler *et al.* (4) suggested that pentazocine might be a useful analgesic and less dangerous than morphine in hypotensive patients.

The present study concerned the possibility that pentazocine might increase blood pressure and heart rate by altering the responses to transmitter amines. This paper reports the effects of pentazocine on the pressor responses to exogenous epinephrine (I) and levarterenol (II).

EXPERIMENTAL

Male Sprague–Dawley rats were anesthetized with pentobarbital sodium, 40 mg/kg ip, combined with atropine sulfate, 1 mg/kg. Animals were artificially respired throughout the experiment with a rodent respirator[1]. The right carotid or femoral artery was cannulated with polyethylene tubing filled with heparin in saline to facilitate pressure measurements using a pressure transducer[2]. The right femoral vein was cannulated for intravenous injections of drugs.

Pressure changes were analyzed by planimetric measurement of the area, in square centimeters, under the dose–mean blood pressure response curve and by measurement of the time, in seconds, for the mean blood pressure response to return half-way to the control value. Statistical analysis was performed by using the analysis of variance combined with Duncan's new multiple range test (5). Levarterenol bitartrate[3] and epinephrine bitartrate[3] solutions were prepared from stock solutions on the day of use. Pentazocine[4] was dissolved in acidic aqueous solutions prior to use. All doses are reported as the salt.

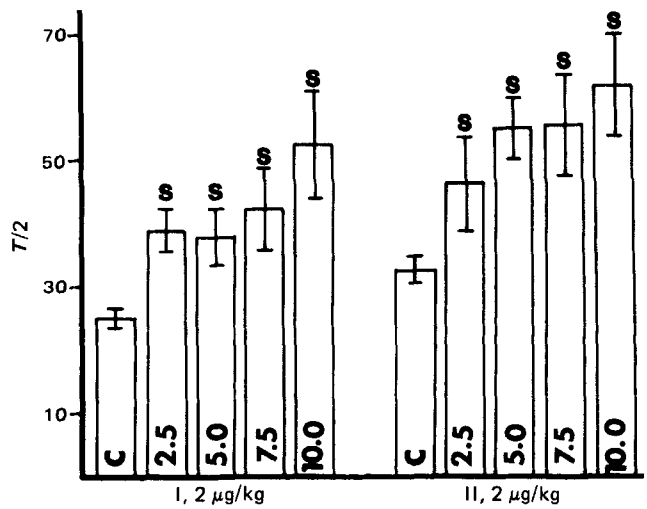

Figure 1—*Effect of intravenous pentazocine (milligrams per kilogram shown in the bars) on the duration (T/2, in seconds) of the pressor responses to I and II. All doses of pentazocine significantly (S) potentiated the duration of the pressor responses to I and II when compared to the control (C) at* $p < 0.05$.

RESULTS AND DISCUSSION

Epinephrine, 2 μg/kg, and levarterenol, 2 μg/kg, were given intravenously to rats to determine control blood pressure responses. Pentazocine was given in 2.5-mg/kg increments intravenously until a total dose of 10 mg/kg had been administered. The intravenous administration of pentazocine routinely depressed the blood pressure, but the depression was transient and the blood pressure was allowed to return to control levels before the agonists were given.

After each dose of pentazocine, the agonists were again administered and the responses were measured and compared to control responses. All doses of pentazocine significantly increased the duration of the pressor responses to epinephrine and levarterenol (Fig. 1), while the area under the dose–response curve of these two amines was significantly increased only after a 10-mg/kg dose (Fig. 2).

Since these experiments involved a long period and several injections per animal, a study was conducted to evaluate the possibility that the responses to epinephrine and levarterenol might be increased by some sort of autopotentiation instead of an action by pentazocine. Blood pressure responses to four doses of epinephrine were obtained several

[1] Harvard Apparatus Co. model 680.
[2] Statham P23AC.
[3] Sigma Chemical Co., St. Louis, Mo.
[4] Talwin, Sterling-Winthrop Research Institute.

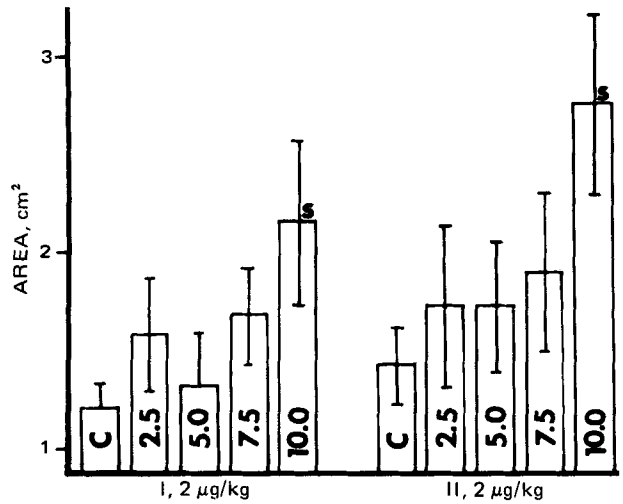

Figure 2—*Effect of intravenous pentazocine (milligrams per kilogram shown in the bars) on the pressor responses to I and II. At a dose of 10 mg/kg, pentazocine significantly (S) potentiated the pressor response to I and II when compared to the control (C) at* $p < 0.05$.

times. No autopotentiation was found; in fact, the responses tended to decrease after the agonist had been administered several times[5].

Tammisto *et al.* (6) reported a marked increase in plasma catecholamine levels after an intravenous injection of pentazocine, 1.2 mg/kg, in humans. The rise in plasma catecholamine levels was concomitant with the rise in blood pressure and heart rate in the same patients. It was concluded that the rise in circulating catecholamines was due to peripheral release of epinephrine and levarterenol caused by central sympathetic stimulation by pentazocine. These investigators also suggested that the pentazocine-induced increase in plasma catecholamines was not due to an inhibition of reuptake or of enzymatic degradation of the catecholamines since pentazocine did not potentiate the pressor responses of exogenous epinephrine or levarterenol.

The results presented in this study do not agree with those of Tammisto *et al.* (6). Pentazocine potentiated the pressor responses of exogenous amines. It is tempting to suggest that one possible explanation for the pentazocine–pressor amine interaction would be a pentazocine-induced alteration of the physiological disposition of the neurotransmitters by interaction with the sympathetic nervous system.

Investigations into the actions of pentazocine on neural function in the central nervous system support the hypothesis that pentazocine may alter adrenergic function.

Holtzman and Jewett (7) demonstrated that pentazocine, at a wide range of doses, significantly lowered rat brain norepinephrine and theorized that the drop in brain norepinephrine content might be related to a pentazocine-induced release of the adrenergic transmitter. Likewise, Paalzow *et al.* (8) reported a drop in rat brain norepinephrine after pentazocine treatment. They also showed that pentazocine accelerated the depletion of the adrenergic neurotransmitter in the brain after tyrosine hydroxylase or dopamine β-hydroxylase was inhibited, thereby indicating that the turnover of norepinephrine was increased.

[5] Unpublished results.

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Synthesis and Hydrolysis of Fluorene-9-spiro-2′-(*N*-aryl-3′,3′-dichloroaziridines)

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Abstract □ The synthesis of eight fluorene-9-spiro-2′-(*N*-aryl-3′,3′-dichloroaziridines) was achieved *via* the reaction of dichlorocarbene with the appropriately substituted *N*-fluorenylideneanilines. Hydrolysis of the spirofluorenes afforded the corresponding 9-chlorofluorene-9-carboxanilides in excellent yields.

Keyphrases □ Fluorene-9-spiro-2′-aziridines, various—synthesized, hydrolyzed to 9-chlorofluorene-9-carboxanilides □ Aziridines, fluorene-9-spiro—synthesized, hydrolyzed to 9-chlorofluorene-9-carboxanilides □ Hydrolysis—various fluorene-9-spiro-2′-aziridines to 9-chlorofluorene-9-carboxanilides □ Spiro compounds—various fluorene-9-spiro-2′-aziridines synthesized, hydrolyzed to 9-chlorofluorene-9-carboxanilides

The synthesis of aziridines from imines has been accomplished either by the reactions of imines with dimethylsulfoxonium methylide in dimethyl sulfoxide (1) or by the insertion of carbenes in the carbon–nitrogen double bond of imines (2, 3).

The reaction of *N*-fluorenylideneanilines (I) with dimethylsulfoxonium methylide afforded a mixture of the starting imine and fluorenone instead of the expected spiroaziridines. However, the reactions of I with dichlorocarbene, generated by the reaction of chloroform with