NICOTINE CONVULSIONS AND THEIR MODIFICATION BY RESERPINE AND CHLORPROMAZINE

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The effect of reserpine and chlorpromazine on nicotine convulsions was studied in rats. Reserpine facilitated nicotine convulsions. The effect of reserpine was related to its dose. Chlorpromazine on the other hand had a protective action against nicotine convulsions, the effect being proportional to the dose of chlorpromazine. The probable mechanism of the protective action of chlorpromazine is discussed. Intracerebral injection of minute quantities (1 to 4 μg) of nicotine caused instantaneous convulsions in mice. The possible implication of this finding is also discussed.

The relationship of reserpine and chlorpromazine to the various convulsant and anticonvulsant drugs has been extensively investigated. Thus it is known that reserpine exacerbates some aspects of the convulsions produced in mice by injection of leptazol and caffeine and lowers the threshold for electro-shock seizures. On strychnine, ammonium acetate or picrotoxin induced maximal tonic extensor seizures in mice, however, reserpine has a supperssive effect (Chen *et al.*, 1954; Chen and Ensor, 1954; Chen and Bohner, 1956). Reserpine also antagonises the anticonvulsant activity of phenytoin, various barbiturates and myanesin (Chen and Bohner, 1956). A number of clinical investigators have reported the occurance of convulsive seizures in non-epileptic patients undergoing intensive therapy with phenothiazine derivatives (Feldman, 1957; Voegele and May, 1957). In experimental animals Heming *et al.*, (1956) and Tedeschi *et al.*, (1958) observed a minimal electro-shock seizure threshold lowering effect after chlorpromazine administration. Increased tendency to convulsions after chlorpromazine has also been reported in monkey made "epileptic" by implantation of alumina cream (Drill, 1958). However, to our knowledge there are no reports describing the effect of reserpine and chlorpromazine on nicotine convulsions. The present report describes the effect of reserpine and chlorpromazine on nicotine convulsions in rats. Certain other observations which might shed some light on the nature of nicotine convulsions are also included.

METHODS

Unanaesthetized rats of either sex weighing between 130 to 200 g were used as experimental animals. Nicotine was injected intraperitoneally as a solution containing 1.0 mg base/ml saline. The convulsions developed within 2 to 3 mins after the injection of nicotine and their nature varied with the dose employed. A small dose caused coordinated running movements of the front legs only, while a larger dose caused similar movements of the hind legs also. A convulsion was recorded only when the movements affected all four legs. Fifty rats were given three different doses of nicotine (1.0 mg/kg, 1.25 mg/kg and 1.5 mg/kg) and a dose response curve was obtained by plotting the convulsion rate in probits against long dose of nicotine.

In a few pilot experiments it was found that reserpine facilitated nicotine convulsions while chlorpromazine antagonised them. The effect of reserpine was, therefore, studied against the CD_{20} (convulsive dose 20) of nicotine while the effect of chlorpromazine was studied against the CD_{99} (convulsive dose 99) of nicotine.

Reserpine and chlorpromazine in different doses were injected intraperitoneally 2 hrs and ½ hr respectively before the challenging dose of nicotine.

Intracerebral injection of nicotine in conscious mice.—Twenty-five male albino mice weighing between 20 to 25 g were used. Nicotine in Locke solution was injected intracerebrally according to the method of Haley and McCormick, (1957).

Doses of nicotine and reserpine are in terms of the base. Chlorpromazine was used as chlorpromazine hydrochloride and the doses refer to the salt.

RESULTS AND DISCUSSION

Nicotine convulsions.—Nicotine can be given intravenously in mice to produce convulsions (Laurence and Stacey, 1952). However, the convulsant dose of nicotine varies considerably with the rate of injection which has to be accurately timed to get a consistent response. In rats nicotine is usually given subcutaneously ; but the convulsions take a long time to develop (about 15 min). Nicotine was, therefore, tried intraperitoneally. Administered by this route, nicotine produced convulsions within 2-3 min and it was possible to get a dose response relationship.

In Fig. 1 the convulsion rate in probits is plotted against the log dose of nicotine. The CD_{50} (convulsive dose 50) was calculated by the method of Miller and Tainter (1944) and was found to be 1.15 ± 0.15 mg/kg. CD_{99} and CD_{20} were computed from the regression line and were 1.9 mg/kg and 1.0 mg/kg respectively.

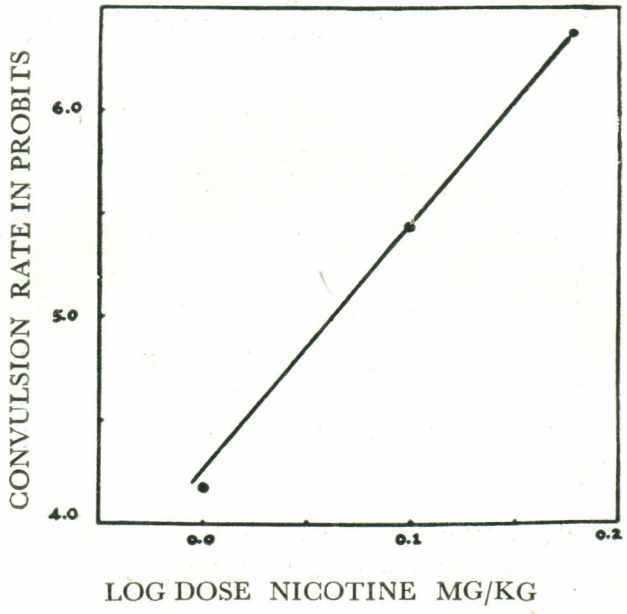

Fig. 1. Dose-response curve of the convulsant effect of nicotine in rats. Nicotine was injected intraperitoneally in saline in doses of 1.0 mg/kg, 1.25 mg/kg and 1.5 mg/kg.

After an adequate dose of nicotine the "convulsive episode" lasted for 2 to 3 min and consisted of the following events occuring in the order mentioned: hyperventilation, running movements of all legs, a period of apnoea, and a state resembling an akinetic seizure during which the animals looked stunned, were immobile but were hypersensitive to sound or touch.

Effect of reserpine on nicotine convulsions.—Reserpine facilitated nicotine convulsions. Thus the convulsion rate after the CD_{20} of nicotine increased when the animals were pretreated with reserpine. This "facilitation" action of reserpine was related to its dose.

In Fig. 2 the convulsion rate after the CD_{20} of nicotine in probits was plotted against the log dose of reserpine. It was not entirely unexpected that reserpine would facilitate nicotine convulsions because it is known that reser-

pine potentiates the convulsant action of leptazol, nikethamide and caffeine. The exact nature and significance of this "facilitation" action of reserpine is quite unknown.

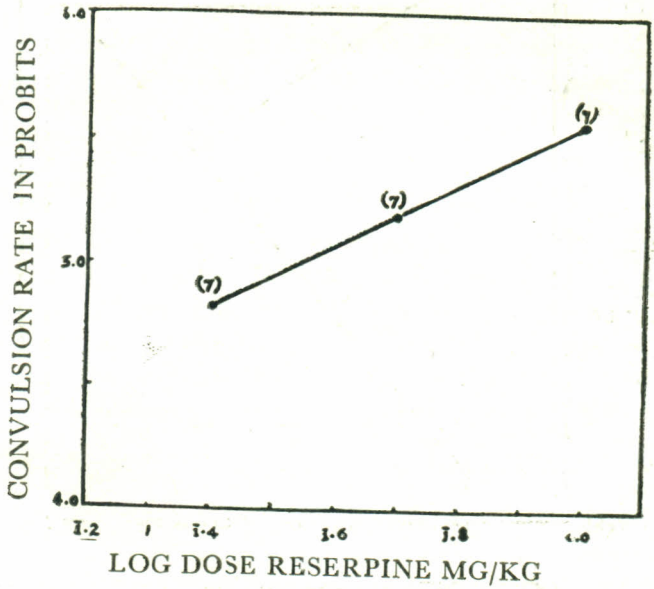

Fig. 2. Effect of reserpine (0.25 mg/kg, 0.5 mg/kg and 1.0 mg/kg) on the convulsion rate in rats after the CD_{20} of nicotine. Reserpine was injected intraperitoneally in saline 2 hr before the challenging dose of nicotine. The figures in the parentheses indicate the number of animals used for each observation.

Effect of chlorpromazine on nicotine convulsions.—Chlorpromazine exerted a protective action against nicotine convulsions in rats. Thus the convulsion rate after the CD_{99} of nicotine progressively decreased when the animals were pretreated with increasing doses of chlorpromazine.

In Fig. 3, the convulsion rate after the CD_{99} of nicotine in probits is plotted against the log dose of chlorpromazine. It is unlikely that the protective action of chlorpromazine is due to the central action of the drug because chlorpromazine is known not to have any anticonvulsant action against leptazol. Moreover, the site of the convulsant action of nicotine is probably the motor cortex (Rizzolo, 1929) while chlorpromazine acts predominantly on the more caudal levels of the brain like the reticular formation of midbrain and diencephalon and the amygdaloid nuclei (Schallek *et al.*, 1956 ; Preston 1956).

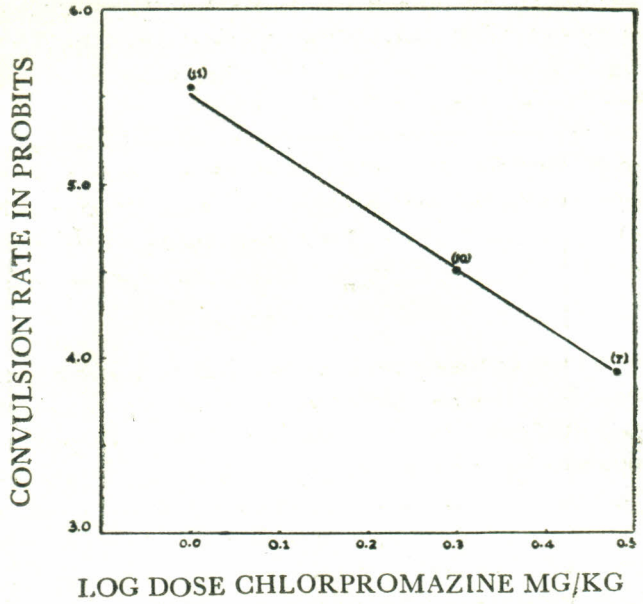

Fig. 3. Effect of chlorpromazine (1.0 mg/kg, 2.0 mg/kg and 3 mg/kg) on the convulsion rate rats after the CD_{99} of nicotine. Chlorpromazine was injected intraperitoneally in saline 1/2 hr before the challenging dose of nicotine. The figures in the parentheses indicate the number of animals used for each observation.

Laurence and Stacey (1953) have demonstrated that hexamethonium, dibenamine, yohimbine, ergotamine and dihydroergotamine protect mice and rats against nicotine convulsions. Mecamylamine and pempidine are also known to protect against nicotine convulsions (Stone *et al.*,1956: Spinks *et al.*, 1958). Laurence and Stacey (1953) concluded that the convulsant action of nicotine is increased by the sympathetic stimulation that it causes and that substances like hexamethonium or dibenamine which protect against nicotine do so by diminishing those effects of nicotine caused by sympathetic stimulation. Other convulsants in whose action sympathetic stimulation does not play an important part were not antagonised by hexamethonium.

A similar situation seems to exist as regards chlorpromazine which protects against nicotine convulsions but has no action against leptazol. Chlorpromazine has an antiadrenaline action and is known to reduce the blood pressure rise after nicotine in spinal cats (Kopera and Armitage, 1954). It is quite likely that the protective action against nicotine may be due to the antiadrenaline property of chlorpromazine.

Intracerebral injection of nicotine in conscious mice.—Intracerebral injection of minute amounts (1 to 4 μg) of nicotine caused immediate and sometime violent convulsions in mice. This action of nicotine was dose related. The intracerebral CD_{50} of nicotine was calculated according to the method of Miller and Tainter (1944) and was found to be 1.0 $\pm$ 0.52 μg.

After an effective dose of nicotine, convulsions occured as soon as the drug was administered and were followed by hyperventilation and a period of hyperexcitability lasting for about 4 to 6 min during which the animals were hyperexcitable to tactile and auditory stimuli. None of the animals showed apnoea.

The mechanism by which nicotine provokes convulsions has not been finally settled. Local application to the motor cortex produces clonic convulsions (Rizzolo, 1929), but it has been suggested that convulsions caused by nicotine administered systemically might by wholly or in part due to anoxia resulting from respiratory arrest; or to stimulation of the carotid body (Lendle and Ruppert, 1942). In the present experiments in each of a total of 97 convulsive episodes occuring after an intraperitoneal injection of nicotine under different experimental conditions (control and reserpine or chlorpromazine pretreated animals) convulsions always occured during the period of hyperventilation and preceded the period of apnoea but never followed it. Moreover, in those instances where chlorpromazine afforded protection against the CD_{99} of nicotine, apnoea was not only present but was slightly prolonged. Respiratory arrest after nicotine is largely due to a peripheral curariform action of the drug (Goodman and Gilman, 1955). Chlorpromazine has a paralytic action on skeletal muscle (Kopera and Armitage, 1954). The prolongation of apnoea in chlorpromazine pretreated animals might be due to a summation of the depressant effects of nicotine and chlorpromazine on the skeletal muscle. Secondly, whenever an intracerebral injection of nicotine produced convulsion it was never preceded or followed by apnoea. Thus it could be shown that apnoea can occur without convulsions and that convulsions can occur without apnoea. Apnoea or respiratory arrest can not, therefore, be the cause of nicotine convulsions. From the present investigation it is difficult to say what part, if any, carotid body stimulation plays in the genesis of nicotine convulsions.

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