PHENAMINE POTENTIATION AND AMINAZINE PREVENTION OF RESERPINE INTOXICATION IN RATS

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We have shown that adrenalectomy greatly lowers the resistance of rats to reserpine. Intoxication and death is much more frequent in adrenalectomized animals than in intact ones. In the latter, reserpine intoxication lasts several days; no special study of its symptoms has been made to date. Intoxication usually develops very rapidly in adrenalectomized rats, death usually occurring 2-4 h after the reserpine is administered. The whole picture of intoxication can therefore be seen in a short period in adrenalectomized rats. The extraordinary resemblance of acute reserpine and serotonin intoxications suggests that acute reserpine poisoning is essentially acute intoxication by endogenic serotonin, liberated from the tissues by reserpine.

Preparations which block monoamine oxidase (which inactivates catechol amines and serotonin) are known to increase the toxicity of serotonin [4, et al.]. We therefore attempted to raise the toxicity of reserpine by preliminary administration of Phenamine which, besides its direct stimulation of the adrenergic structures, blocks monoamine oxidase [8]. We also attempted to prevent death by reserpine poisoning with preparations having antiserotonin effects. The preparations selected for this purpose were Aminazine and Sympatholytin [3,7,14,17,18].

EXPERIMENTAL RESULTS AND METHODS

Experiments were performed on 155 adult male rats weighing 130-160 g, taken from the same nursery. All the preparations were injected intraperitoneally as aqueous solutions: Phenamine and reserpine, simultaneously; Aminazine or Sympatholytin, 30 min before administration of the first two. All the preparations were used in doses which did not cause death in the control animals.

As Table 1 shows, the Phenamine injection increased the toxicity of reserpine. We observed a distorted picture of reserpine intoxication; instead of depression, extremely high locomotor excitation was observed. The long excitation period was followed by a shorter period of central nervous system (CNS) inhibition; the rat lay on its side breathing heavily and slowly, and sometimes exhibited tonic convulsions. Death from respiratory arrest occurred after 4 to 6 h, 24 h at the most.

As Table 2 shows, preliminary administration of Aminazine kept rats administered the lethal combination of reserpine and Phenamine alive. Preliminary administration of Sympatholytin did not.

Brodie et al. [5, 6, 16] and other researchers [13], have shown that reserpine both liberates accumulated noradrenalin and serotonin from tissues and prevents binding by the tissues of newly synthesized amines. Since serotonin is synthesized much more rapidly than catechol amines [6, 10], the concentration of newly synthesized serotonin should be considerably higher than that of noradrenalin. In this connection, Brodie proposes that the central effects of reserpine are due to the liberation of serotonin and disturbance of its bonds effected by this substance [6].

Serotonin is inactivated primarily by monoamine oxidase, while catechol amines are inactivated by other means as well, including by "O-methylranspherase" [2, 8]. Observations indicating that monoamine oxidase inhibitors vigorously potentiate serotonin's effects but show little influence on the effects of catechol amines [8], are therefore no surprise. Thus, one can assume that the increase in reserpine toxicity observed when Phenamine is administered simultaneously is because the inactivation of the endogenic serotonin liberated by reserpine is disturbed.

That Aminazine prevents the effects of administered serotonin has been generally established for the peripheral

TABLE 1. Phenamine Potentiation of Reserpine Toxicity

Phenamine (μg/g)	Reserpine (μg/g)	No. of animals in expt.	died	survived
30	–	10	0	10
–	4	20	0	20
2	4	5	0	5
5	4	5	0	5
10	4	5	2	3
15	4	5	3	2
20	4	15	13	2
25	4	5	5	0
30	4	5	5	0

TABLE 2. Effect of Preliminary Aminazine or Sympatholytin Administration on Reserpine and Phenamine Intoxication of Rats

Phenamine (μg/kg)	Reserpine (μg/kg)	No. of animals	Preliminary administration of: μg/g Aminazine	Preliminary administration of: 10-20 μg/g Sympatholytin
15	4	3/5	0/5	–
20	4	4/5	0/5	–
25	4	5/5	0/5	5/5
30	4	5/5	0/5	10/10

Note: Numerator, number of animals which died; denominator, number of animals in experiment.

organs: prevention of nictitating membrane contractions in a cat [14], prevention of bronchospasm with inhalation of serotonin aerosol [3], removal of serotonin-induced increased vascular permeability [18], etc. Aminazine, therefore, reduces the toxicity of subcutaneously administered serotonin [7].

No investigation has yet been made of the antagonism between endogenic serotonin and Aminazine, particularly in the CNS. Death caused by the combined administration of Phenamine and reserpine is attended by signs of CNS inhibition. We believe the cause of death in these cases to be intoxication by endogenic serotonin, and its prevention by Aminazine to be due to the central antagonism between these substances.

On the basis of the data obtained, one can assume that the central effect of Aminazine is associated with an antiserotonin, as well as with a sympatholytic, effect [6].

Unlike Aminazine, Sympatholytin does not prevent death from the combined administration of Phenamine and reserpine. This shows that there are differences in the effects produced by Aminazine and Sympatholytin, although both preparations block the effects of exogenous adrenalin and serotonin [3,6,15,17].

As the data in this paper indicate, Phenamine increases the toxic effect of reserpine, despite the fact that, like other monoamine oxidase inhibitors, it is often used in psychiatric practice as a reserpine antagonist [1,11]. Aminazine, however, which is used in psychiatric practice as a synergist of reserpine [12,13], prevents death from intoxication by reserpine potentiated with Phenamine.

SUMMARY

In the previous paper a supposition was made that acute reserpine poisoning mainly comes to the endogenic serotonin poisoning. This work demonstrates the following: a) phenamine increases the reserpine toxicity; this is attributed to depressed inactivation of endogenic serotonin liberated by reserpine; b) aminazine prevents the death of rats from the fatal reserpine-phenamine combination; this effect is attributed to the central antagonism between aminazine and serotonin; c) sympatholytin does not prevent death resulting from combined phenamine-reserpine administration; this points to the different effects of sympatholytin and aminazine, although both provoke not only the adrenolytic, but also the antiserotonin effect. The significance of these data for psychiatry is emphasized.

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