

ACTION OF RESERPINE ON THE DIGESTIVE TRACT OF EXPERIMENTAL ANIMALS

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The action of reserpine is now explained mainly by a decrease in the content of biogenic amines, especially of serotonin and catecholamines, in the central nervous system and at the periphery. This decrease in the content of these amines in the tissues lasts for a comparatively long time, for several hours depending on the dose of reserpine given. Consequently, on repeated administration reserpine can no longer cause stimulation of the functions activated in response to the first dose of this alkaloid. These functions include the secretory and motor activity of the digestive organs.

The object of the present investigation, conducted on rats, was to discover whether the repeated administration of reserpine produces the same laxative action as the primary administration. The relationship between the hypotension developing after administration of reserpine and the degree of increase in motor activity of the digestive organs was assessed in rabbits.

Besides reserpine, its analogue methoxyphenoserpine [the (-)-methyl ester of O-(p-methoxyphenoxycetyl)reserpinic acid] was also investigated. This substance resembles reserpine closely not only in chemical structure, but also in pharmacological action [6, 11].

EXPERIMENTAL METHOD

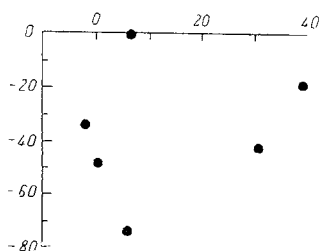
The laxative action of reserpine was investigated in male Wistar rats weighing 150-200 g by the method previously described [6], using phenol red as color indicator of the rate of passage through the gastrointestinal tract. Reserpine was given on the 1st, 3rd, and 5th days of the experiment in a dose of 0.25 mg, which had a laxative effect in most animals when given on the first day. The laxative action was assessed until 6 h after intraperitoneal injection. On the 6th day methoxyphenoserpine was injected in a dose causing a laxative effect in more than 50% of the animals.

The simultaneous measurement of the blood pressure and motor activity of the digestive organs to assess the relationship between these two functions was carried out on chinchilla rabbits of both sexes weighing 2-3 kg, anesthetized with urethane. The blood pressure was measured in the femoral artery. The gastric motility was measured by a water manometer by introducing a balloon through the anterior wall of the stomach. The kymographic tracing was made by means of a rotating cartographic measuring apparatus [7, 9]. Neostigmine was injected intravenously in a dose of 12.5 μ g/kg into both the control and experimental animals 30 min before the injection of reserpine [7]. Reserpine was injected in a dose of 1 mg/kg, producing a significant increase in the motor activity of the stomach and a well marked fall of blood pressure for a period of 2 h.

EXPERIMENTAL RESULTS AND DISCUSSION

The first and second injection of reserpine produced a laxative effect in 9 of the 10 experimental rats. After the 3rd intraperitoneal injection of reserpine in a dose of 0.25 mg/kg the sensitivity of the animals to the drug fell sharply, and a laxative effect was observed in only one animal. A similar loss of sensitivity was observed in relation to the reserpine analogue, methoxyphenoserpine, injected in a dose producing a laxative effect in more than 50% of normal experimental animals. A similar phenomenon was observed in the other experiments in which methoxyphenoserpine was injected intraperitoneally 3 times (on the 1st, 3rd, and 5th days) in a dose of 10 mg/kg while on the 6th day after intraperitoneal injection of reserpine in a dose of 0.25 mg/kg, disappearance of the laxative effect was noted. The 3rd injection of methoxyphenoserpine, i.e., on the 5th day of the experiment, likewise had no laxative action.

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Relationship between gastric motility and blood pressure 90 min after injection of reserpine into rabbits anesthetized with urethane. Along the axis of abscissas, changes in motility (in % of initial value; increase); along the axis of ordinates, changes in blood pressure during the same time interval (in % of initial value; decrease). The circles denote individual animals.

As the figure shows, no correlation was found between the changes in the blood pressure and the changes in motor activity of the stomach (coefficient of correlation $r = -0.159$). Similar results were obtained after administration of methoxyphenoserpine.

Disappearance of the laxative action of reserpine during its repeated administration has not hitherto been studied. Some investigators [1] found that the secretory response in dogs disappeared 24 h after intraperitoneal injection of 0.1 or 0.2 mg/kg reserpine. Others [2], studying gastric secretion in man, also observed blocking of the action of reserpine after daily intramuscular injection of reserpine in doses of 1 mg for 10 days, on the 11th day. Probably some analogy may exist between the changes in gastric secretion [1, 2] and the motor or laxative changes (the result of the present experiment). However, the dissociation between the changes in gastric secretion and gastric motility must be noted after administration of therapeutic agents [5]. The author has observed differences in the threshold of sensitivity of the gastric secretion [6] and the movements of the gastrointestinal tract [8] in re-

lation to reserpine. Changes in motor activity were apparent in rats after administration of 0.5 mg/kg reserpine, whereas changes in gastric secretion only appeared after administration of a dose 5-10 times larger [6].

The discovery of dissociation between the degree of fall of the blood pressure and the changes in the motor activity of the stomach in rabbits anesthetized with urethane in response to the action of reserpine may be evidence of differences in the mechanism of the changes produced by reserpine in the cardiovascular system and in the gastrointestinal tract. Malhotra and co-workers [3, 4] likewise found no connection between the tranquilizing action, the degree of bradycardia, and the laxative effect of reserpine in dogs.

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