Cardiovascular Response of the Anesthetized Hamster to Reserpine and Ganglionic Blockade

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The changes produced by reserpine and the ganglionic blocking agent, chlorisondamine chloride on the blood pressure, peripheral flow and blood vessel caliber of the hamster have been studied in an attempt to determine the first cause of the hypotensive effect of these compounds.

CIRCULATORY responses to ganglionic blocking agents are reported to vary with the level of arterial pressure, state of anesthesia, rate of administration, dose, route and frequency of administration and according to the etiology of the hypertension. Vascular responses to reserpine have been reported to vary with the level of blood pressure and state of anesthesia. Nevertheless, in the responsive hypertensive human and in the normotensive anesthetized laboratory animal, these agents interfere with some cardiovascular activity which is required for sustaining blood pressure, thus producing a decline in blood pressure and, further, act to prevent compensation by the several mechanisms which are normally brought into play to restore a reduced arterial pressure. The specific cardiovascular mechanism by which these two drugs initiate blood pressure decline have not been unequivocally elucidated.

We therefore decided to study directly the effects of these two agents on peripheral circulation in the hope that observed effects on flow, vessel size and blood pressure might help to determine the first cause of the vascular actions of these compounds.

METHODS

Male golden hamsters weighing 80 to 100 Gm. were used in this study. The method of Lutz and co-workers was employed except that the pouch was not cut to facilitate observation of the vessels and was kept moist with physiologic saline. Photomicrographs were taken at .1 sec exposure time.

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Cinephotomicrographic recordings of the circulation of the pouch were taken with 16 mm. Anscochrome film.

Measurements of vessel calibers were made with the Bausch and Lomb Filar micrometer which had been calibrated with a Bausch and Lomb stage micrometer.

Blood pressures were taken by direct cannulation of the carotid arteries under barbiturate anesthesia by the method of Pradhan and co-workers and recorded through the Sunborn electronanometer and Polyviso.

RESULTS

Effect of Anesthesia on Circulation and Survival. Five animals were anesthetized with 80 mg./Kg. sodium pentobarbital intraperitoneally and 6 animals with 80 mg./Kg. Dial-Urethane and the circulation of the cheek pouch was observed over a 1 hour period. These anesthetics produced no deleterious changes over this time period as judged by the fact that rapid red cell velocity was maintained in arterioles, venules and capillaries and by the absence of stasis and petechiae.

The combined administration of 80 mg./Kg. of Dial-Urethane intraperitoneally and 0.5 mg./Kg. of reserpine phosphate subcutaneously was lethal by 24 hours to most of the animals tested. However, the combined administration of 80 mg./Kg. sodium pentobarbital intraperitoneally and 0.5 mg./Kg. of reserpine phosphate subcutaneously was not lethal to any of the 10 animals tested; recovery from anesthesia occurred within 1 to 3 hours and from the reserpine within 1 week.

A combination of chlorisondamine chloride, 3 mg./Kg. intraperitoneally, and 80 mg./Kg. of

† A short film prepared in conjunction with these studies and demonstrating the circulatory effects of reserpine and ganglionic blockade described herein will be lent upon request.
Dial-Urethane was not lethal to any of the 10 animals tested. Recovery was complete by the next morning.

**Effect of Reserpine on Circulation.** Reserpine phosphate in doses of 0.25 to 0.5 mg./Kg. was administered subcutaneously to unanesthetized hamsters. These doses were not lethal to the 10 animals studied. By 3 hours mild sedation, ptosis and diarrhea were evident. At 24 hours, when the animals were exhibiting marked sedation, they were anesthetized with 80 mg./Kg. of sodium pentobarbital and the circulation in the cheek pouch was observed. A generalized moderate to marked slowing in red cell velocity in the venules, arterioles and capillaries was observed but little or no stasis occurred. Pulsatile flow was observed in some arterioles and venules in which this phenomenon had not previously been observed. These animals all recovered from anesthesia and within 1 to 2 weeks after the administration of reserpine, when signs of its activity had disappeared, the animals were again anesthetized and the cheek pouch circulation observed. Red cell velocity had returned to that observed before reserpine administration.

Seven animals were anesthetized with pentobarbital, and measurements of arteriole and venous caliber changes were made following administration of 0.5 mg./Kg. of reserpine phosphate. Three anesthetized animals which did not receive reserpine were run simultaneously as controls. Measurements were made over a 4 to 5 hour period. The arterioles studied varied in diameter from 16 to 49 μ. Animals not treated with reserpine exhibited no marked changes in either arteriole or venule caliber. Five of 7 reserpine-treated animals exhibited distinct increases in arteriole diameter after 4 to 5 hours, ranging from 32 per cent to 100 per cent (mean increase, 60 per cent). Venous caliber was increased in only 1 animal.

Since the effects on red cell velocity and vessel size were pronounced, it was decided to measure the blood pressure effects of reserpine in the hamster. Eight animals were given 0.5 mg./Kg. of reserpine subcutaneously, and after 24 hours these animals were anesthetized with pentobarbital and their carotid arteries were cannulated. The pressures of 6 of these animals did not differ markedly from untreated control pressures which lay between 100 and 125 mm. Hg. Two animals exhibited clear-cut hypotension, the mean arterial pressures being 50 mm. Hg for both animals.

**Effect of Ganglionic Blockade on Circulation.** Doses of 0.1 to 3 mg./Kg. of chlorisondamine chloride were administered intraperitoneally to 20 hamsters anesthetized with Dial-Urethane. Within 5 to 10 min. following 1 to 3

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**Fig. 1. Reduction in venous red cell velocity induced by chlorisondamine chloride (3 mg./Kg.), and subsequent recovery. Left, control; middle, 10 min.; right, 35 min. All pictures exposed at .1 sec. Reduction in red cell velocity indicated by granular appearance of center photomicrograph.**
mg./Kg. of chlorisondamine chloride, there occurred a rapidly-developing stasis of small venules (fig. 1), arterioles and capillaries. In many cases there was complete disappearance of capillary flow and emptying of some smaller arterioles and venules. A sluggish flow was maintained in the larger venules and arterioles. Direct measurement of changes in arterioles with diameters of 17 to 72 μ. demonstrated that arteriolar constriction had occurred in 6 out of 8 animals, the decreases ranging between 23 and 38 per cent (mean decrease, 35 per cent). No change in venous diameters was observed. These effects lasted for approximately 10 to 20 min., after which gradual recovery occurred, until by 20 to 30 min., recovery of red cell velocity (fig. 1) and arteriolar caliber was complete. However, in 3 of the 20 animals studied recovery of red cell velocity was only partial.

At doses as low as 0.1 mg./Kg. of chlorisondamine chloride the effects were qualitatively the same but less severe.

Doses of 1 to 3 mg./Kg. of chlorisondamine chloride produced a prompt, sustained decline of 50-75 mm. Hg in arterial pressure in the 5 hamsters tested. In contrast to the recovery of flow observed in the cheek pouch 20 to 30 min. after drug administration, the lowered pressure exhibited no recovery over a 2 to 4 hour period. At the end of this time the injection of dl-amphetamine or norepinephrine produced marked pressor responses and attested to the responsiveness of the circulatory system.

**DISCUSSION**

The vascular alterations observed in the pouch after reserpine administration to anesthetized hamsters are marked but apparently per se not sufficient always to produce clearly-defined falls in blood pressure. It would seem necessary to postulate that simultaneous compensatory adjustments are being produced elsewhere. The nature of these changes is not clear.

The circulatory alterations seen in the pouch after ganglionic blockade are probably the result of the blood pressure fall rather than the cause of it, i. e., they reflect a stagnation and emptying which occurs passively because of changes produced in another part of the vascular system. This is concluded because, while the onset of blood pressure decline and the peripheral slowing occurred simultaneously, no recovery of the blood pressure occurred to parallel the recovery of the flow.

Likewise, the immediate decline in blood pressure is not due to generalized arteriolar vasodilatation since arteriolar narrowing occurs during the decline in pressure. This vasoconstriction could either have been neurogenically or passively induced. Since recovery of the arterioles to normal caliber occurred concurrently with the return of flow at a time when blood pressure was not recovering, the narrowing of the arterioles would seem to have been secondary to vascular emptying.

Slight or no change in peripheral vascular resistance16-16 or in mesenteric resistance1 occurs following ganglionic blockade indicating that the degree of interruption of ganglionic transmission is not always sufficient to produce marked peripheral relaxation. The action of ganglionic blocking agents on the nerve supply to arterioles may be primarily to dampen the increased flow of vasoconstrictor impulses induced by reflex compensatory mechanisms, while the hypotensive activity of these compounds may be exercised at a different site, e. g., venous system.18-21

**SUMMARY**

The effects of reserpine and the ganglionic blocking agent, chlorisondamine chloride on the systemic blood pressure, red cell velocity and blood vessel caliber of the anesthetized hamster have been studied.

Reserpine produces moderate to marked slowing of the red cell velocity in the arterioles, veins and capillaries of the cheek pouch but does not generally produce a marked blood pressure decline. It is inferred that the changes in peripheral circulation as observed in the pouch produce no blood pressure decline because of compensatory adjustments in other beds.

Ganglionic blockade with chlorisondamine chloride rapidly produces stasis in smaller arterioles, venules and capillaries, and marked slowing of red cell velocity in larger arterioles.
and veins concomitantly with a marked decline in blood pressure. Arteriolar narrowing occurred during this decline in pressure. After 10 to 20 min. recovery of red cell velocity and arteriolar caliber ensued and was complete by approximately 30 min. Blood pressure, however, showed no recovery over a period of several hours. It is concluded that the circulatory alterations observed in the pouch represent passive changes induced by the decline in blood pressure. The initial decline in pressure is apparently not due to generalized arteriolar relaxation.

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