New Aspects of Blood Pressure Regulation

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Experiments show that the state of tone and contraction and thus the resistance to stretch of the arterial wall where the pressoreceptors of the carotid sinus are located, are the primary factors affecting these receptors which regulate and moderate reflexly the systemic arterial pressure. Decrease of resistance to stretch of the arterial wall, where the receptors of the sinoaortic nerves which moderate reflexly the general arterial pressure are situated, could be the primary mechanism of essential hypertension.

It is known that the cardio-aortic and carotid sinus pressoreceptor nerves are not only the means of physiologic blood pressure regulation, but also are the reflex buffer or moderator nerves of the arterial pressure. This reflex regulation of blood pressure occurs by the action of arterial pressure itself on receptors located in the vascular walls of the sino-aortic areas.

Experiments of Koch,1 Heymans and co-workers2 and Hauss and associates3 showed that arterial pressure does not act directly on the receptors of the sino-aortic areas, but indirectly by stretching the wall of the arteries where the sino-aortic receptors are located.

These experimental observations suggested that the state of contraction, tone, elasticity and resistance to stretch of the arterial wall of the sino-aortic areas could play a role in the mechanisms of reflex regulation and homeostasis of arterial pressure.

This suggestion has been investigated in a series of experiments in order to examine the influence on arterial pressure and on the reflex homeostasis of blood pressure, of different drugs affecting the tone and resistance to stretch of the arterial wall of the carotid sinus.

METHODS

Dogs were anesthetized with morphine (1 mg. per Kg. subcutaneously) and chloralose (100 mg. per Kg. intravenously). The vagi-aortic nerves were cut in order to limit the reflex regulation and homeostasis of blood pressure to the receptors of the carotid sinuses. The systemic blood pressure was registered with a mercury manometer from a femoral artery. The drugs were applied to the wall of the arteries of the carotid sinus by injection of 2 to 4 ml. of the solutions into the external conjunctival space surrounding both carotid sinus areas.

EXPERIMENTS

It has been shown in a previous group of experiments4 that local application of l-adrenaline hydrochloride, l-noradrenaline hydrochloride, diacetyladrenaline thiosulfonic acid,5 or Pitressin on the carotid sinuses induces a progressive and prolonged fall of the systemic arterial pressure, and decreases or suppresses the hypertensive response provoked normally by the lowering of blood pressure in the carotid sinuses.

These phenomena induced by the local application of adrenaline, noradrenaline or Pitressin on the arterial walls of the carotid sinus are due to a stimulation of the carotid sinus pressoreceptors which moderate reflexly the general arterial pressure. Indeed, section of the carotid sinus nerves, when the arterial pressure has been lowered by local application of the drugs on the carotid sinus areas, provokes an immediate and very marked rise of the systemic arterial pressure.

In another series of experiments,4 drugs known to relax smooth muscles were applied locally to the wall of the arteries of the carotid sinuses. These experiments showed that local application of a small dose of papaverine or benzylimidazoline (Priscoline) on the carotid sinuses causes a reflex rise of systemic arterial pressure. The vasopressor reflexes of carotid sinus origin are maintained and eventually increased. The local application of these drugs on the carotid sinus areas reduces the stimulation...
of the pressoreceptors which moderate reflexly the arterial pressure and consequently induces a rise of systemic blood pressure.

The action on blood pressure of locally applied adrenaline or noradrenaline to the carotid sinus may be reversed by local carotid sinus application of an adrenolytic drug.8

These experiments have been extended mainly in order to determine the threshold dose of adrenaline or noradrenaline able to induce a reflex fall of the systemic arterial pressure by their local action on the carotid sinus areas.

**Fig. 1.** Dog weighing 16.5 Kg. Blood pressure from femoral artery. |1 – |2: clamping and unclamping of common carotid arteries. Between I and II: local application of 2.5 µg. adrenaline on carotid sinuses. II: blood pressure 5 minutes after local carotid sinus application of adrenaline. |3 – |4: clamping and unclamping of common carotid arteries. III: 20 min. after II. |5 – |6: clamping and declamping of common carotid arteries.

This problem has indeed not only a pharmacologic, but also a biologic importance.

**Adrenaline**

l-Adrenaline hydrochloride* in isotonic saline solution was used. Clamping (|1, fig. 1) of the common carotid arteries (hypotension in carotid sinuses) induces, under normal conditions, a marked reflex rise of the systemic arterial pressure. Unclamping (|2, fig. 1) of the carotid arteries (rise of pressure in carotid sinuses) provokes a return to normal systemic arterial pressure.

Local application of 2.5 µg. of adrenaline on each carotid sinus area induces a progressive fall of the systemic arterial pressure (II, fig. 1) and suppresses the hypertensive response (|3 – |4, fig. 1) provoked normally by the decrease of pressure in the carotid sinuses. The systemic arterial pressure returns progressively to normal levels (III, fig. 1) and the hypertensive response induced by clamping both carotid arteries also returns to normal values (|5 – |6, fig. 1), about 20 minutes after carotid sinus application of the small amount of adrenaline.

Local application on the carotid sinus areas of higher doses of adrenaline provokes the same, but still more prolonged, reflex fall of the systemic arterial pressure and a suppression of the normally induced reflex hypertensive response caused by the decrease of pressure in the carotid sinus.

**Noradrenaline**

l-Noradrenaline hydrochloride in isotonic saline solution was used. Clamping (|1, fig. 2) of the common carotid arteries (hypotension in carotid sinuses) provokes, under normal conditions, a marked reflex rise of the systemic arterial pressure. Unclamping of the carotid arteries (|2, fig. 2) induces a reflex return to normal systemic arterial pressure.

Local application of 10 µg. noradrenaline on each carotid sinus area causes only a slight fall of the systemic arterial pressure (II, fig. 2), but induces a marked decrease of the carotid sinus hypertensive reflexes (|3 – |4, fig. 2). About 30 minutes after the local carotid sinus application of noradrenaline, the carotid sinus hypertensive reflexes are again normal (|5 – |6, fig. 2). Clamping (|1, fig. 3) and unclamping (|2, fig. 3) of the common carotid arteries induce the normal reflexes on the systemic arterial pressure. Local application of 200 µg. noradrenaline on each carotid sinus area provokes a marked reflex fall of systemic arterial pressure (II, fig. 3) and a suppression of the carotid sinus reflexes (|3 – |4, fig. 3). About 43 minutes later, the arterial pressure is still low (III, fig. 3) and the carotid sinus hypertensive reflexes are practically absent (|5 – |6, fig. 3). Section (|7, fig. 3) of both carotid sinus nerves provokes an immediate and very marked rise of the systemic arterial

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* Pure l-adrenaline and l-noradrenaline have kindly been supplied by the Sterling-Winthrop Research Institute.
pressure from 80 to 300 mm. Hg. This fact shows again that the local application of noradrenaline on the carotid sinus areas induces a fall of the systemic arterial pressure by increase of the reflex moderating action of the carotid sinus receptors and nerves on the arterial pressure.

Potassium Chloride

Clamping (↑1, fig. 4) and unclamping (↑2, fig. 4) of the common carotid arteries induce the normal reflexes on the systemic arterial pressure.

Local application (↑3, fig. 4) of 40 mg. potassium chloride in 0.4 ml. of water on the carotid sinus areas provokes a marked rise of potassium chloride, the systemic arterial pressure and the carotid sinus reflexes (↑6—↑7, fig. 4) are again normal.

Smaller amounts of 2 to 10 mg. potassium chloride applied to the carotid sinus areas induce similar reactions of reflex rise in systemic arterial pressure.

Dibenamine

As already shown, after local application of the adrenolytic compound, N-(2-bromo-
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Fig. 5. Dog weighing 26 Kg. Blood pressure from femoral artery. 11–12: clamping and unclamping of common carotid arteries. 13: local application of 250 mg. noradrenaline on carotid sinuses. 14–15: clamping and unclamping of common carotid arteries. 16: local application of Dibenamine on carotid sinuses. III: about 15 minutes after II. 17–18: clamping and unclamping of common carotid arteries. 19: section of both carotid sinus nerves.
ethyl)-N-ethyl-l-naphthalene methylamine hydrobromide or SY-28, the local application on the carotid sinuses of l-adrenaline or l-noradrenaline does no more induce a reflex fall, but on the contrary produces a reflex rise of the systemic arterial pressure.

These experiments have been extended to Dibenamine, another adrenolytic drug.

Clamping (\(\uparrow 1\), fig. 5) and unclamping (\(\uparrow 2\), fig. 5) of the common carotid arteries induce the normal carotid sinus reflexes on the arterial pressure.

Local application (\(\uparrow 3\), fig. 5) to the carotid sinus areas of 250 \(\mu\)g. noradrenaline provokes a progressive and very marked reflex fall of arterial pressure. Clamping (\(\uparrow 4\), fig. 5) and unclamping (\(\uparrow 5\), fig. 5) of the carotid arteries elicit no more changes in arterial pressure.

Local application (\(\uparrow 6\), fig. 5) on the carotid sinuses of 2.5 ml. Dibenamine, 1 per cent, provokes a progressive return of blood pressure to normal levels and restores the carotid sinus reflexes (\(\uparrow 7\)–\(\uparrow 8\), fig. 5). Section (\(\uparrow 9\), fig. 5) of both carotid sinus nerves induces a marked rise of arterial pressure.

Similar observations were made with adrenaline.

Local application of dihydroergotamine* on the carotid sinus areas also reverses the effects of locally applied adrenaline and noradrenaline.

**DISCUSSION**

These experiments show that drugs such as adrenaline, noradrenaline and Pitressin, which are known\(^7\) to induce a contraction of the arterial wall, applied to the carotid sinus areas, cause a stimulation of the receptors of the carotid sinus nerves which moderate reflexly the systemic arterial pressure. This stimulation of the carotid sinus pressoreceptors induces reflexly a fall of the systemic arterial pressure and decreases or suppresses the hypertensive reflexes normally provoked by decrease of blood pressure in the carotid sinus.

These influences on systemic blood pressure and carotid sinus reflexes of adrenaline and noradrenaline applied locally to the carotid sinus areas are decreased, suppressed or reversed by local application on the carotid sinuses of an adrenolytic drug.

Papaverine, Priscoline and potassium chloride, applied to the arterial wall of the carotid sinus areas, provoke the opposite reactions which are characterized by a reflex rise of the systemic arterial pressure and an increase of the carotid sinus hypertensive reflexes.

These experimental observations thus demonstrate that the state of contraction and the resistance to stretch of the arterial wall where the receptors of the regulator and moderator nerves of blood pressure are located are the primary factors affecting these receptors.

These experiments also show that not increase\(^8\) but decrease of tone and resistance to stretch of the wall of the arteries where the receptors of the moderator nerves of blood pressure are located could be the primary mechanism of essential hypertension.

As the experimental observations show that very small amounts of adrenaline or noradrenaline applied to the carotid sinus areas are effective, and as it has been shown\(^10\) that the walls of arteries contain considerable amounts of adrenaline and noradrenaline, it may be suggested that these biologic substances play a role in the maintainance and regulation of the intrinsic tone and resistance to stretch of the arteries where the pressoreceptors are located, and thus have a part in the mechanisms of the reflex homeostasis of blood pressure.

**SUMMARY**

1. Small amounts of adrenaline or noradrenaline applied to the arterial wall of the carotid sinus areas induce a stimulation of the pressoreceptors and thus a marked and prolonged reflex fall of the systemic arterial pressure and a decrease or suppression of the hypertensive reflexes normally provoked by a decrease of pressure inside of the carotid sinus.

2. Section of the carotid sinus nerves when the systemic arterial pressure has been lowered by the local application of adrenaline or noradrenaline on the carotid sinus areas causes an immediate and very marked rise of the systemic arterial pressure.

3. Local application on the carotid sinus of the adrenolytic drugs Dibenamine or dihydroergotamine has been kindly supplied by Sandoz Laboratories (Basel).

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* Dihydroergotamine...
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glycine suppresses and reverses the effects of locally applied adrenaline and noradrenaline to the carotid sinus areas.

4. Potassium chloride applied to the carotid sinus areas induces a reflex rise of systemic arterial pressure and an increase of the hypertensive carotid sinus reflexes.

5. These experiments show that the state of contraction and thus the resistance to stretch of the arterial wall where the pressoreceptors are located are the primary factors affecting these receptors which regulate and moderate reflexly the systemic arterial pressure.

6. The physiologic and pathologic significance of these experimental observations are discussed.

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