THE INFLUENCE OF PRESSOR AND DEPRESSOR SUBSTANCES ON THE GREATER AND LESSER CIRCULATIONS IN HYPOXIC HYPOXIA

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The problem of autonomic tone during oxygen lack is one of great interest. Many investigators have shown that in hypoxic hypoxia, there is a great reduction of sensitivity to adrenalin [8, 10]. The explanation of these authors is that in hypoxia the excitability of the sympathetic nerves is reduced [3, 7]. In experiments on animals and from observations on human subjects it has been shown that hypoxia leads to a progressive increase of sensitivity to acetylcholine, and that this increase occurs with the vagus nerves either intact or divided [1, 4, 6, 7].

The object of the present investigation has been to study the influence of pressor and depressor substances on the greater and lesser circulations in hypoxia, during hypocapnia, and during normal breathing.

METHOD

Acute experiments were performed on 38 adult dogs weighing 6 - 12 kg, under ether anesthesia, while normal respiration was maintained. A tracheotomy cannula was inserted into the trachea; to separate the expired and the inspired air, it was fitted with a valve. During the experiment, the valve connected the cannula to a Douglas bag which had previously been filled with the appropriate gaseous mixture. We used three mixtures: 1) nitrogen with 10% oxygen, 2) nitrogen with 4 - 5% oxygen, and 3) nitrogen with 4 - 5% oxygen and 1 - 3% carbon dioxide. The composition of the mixture was checked on a Haldane apparatus. The degree of oxygen lack was measured by oxidizing the arterial blood in an oxyhemometer, the sensitive element of which was fixed to the ear of the animal. Records of the pressure in the pulmonary artery were made by a tube introduced into it through the jugular vein; during its insertion the thoracic cavity remained closed, and control was supplied by an x-ray apparatus. Pressure in the greater circulation was recorded by a tube fixed into the carotid artery. The pressures were directly recorded by a 6-channel Al'var Kardiovar apparatus connected to a "Barovar" electromanometer. When air was breathed, in hypoxia with hypocapnia, and during normal breathing, 0.7 μg/kg of adrenalin or 5 - 10 μg of acetylcholine was injected into the femoral vein. When various degrees of hypoxia had been established, and during hypocapnia, 10 - 15 μg/kg of serotonin was injected into the femoral vein.

In our previous experiments [2], we showed that during hypocapnia, with a moderate degree of hypoxia, or with normal breathing and a considerable degree of hypoxia, there were two phases of the circulatory reaction: 1) a period of maximum hemodynamic change, and 2) an adaptation to the hypoxia. During more profound hypoxia, and when there was hypocapnia, the maximum hemodynamic change was maintained, but it did not change over into the phase of adaptation, and serious circulatory changes resulted. In the present investigation, all the substances to be studied were injected during the second phase of hypoxia.

RESULTS

Acetylcholine. The injection of acetylcholine while the animal was breathing air always induced a depressor response in the greater circulation, a variable effect in the lesser, and a slight increase of heart and respiration rates (Fig. 1, A). The pressure in the greater circulation fell on average by 12 - 15mm mercury, the number of respiratory movements increased by 2 - 3 per minute, and the heart rate by 15 - 20 beats per minute.

The injection of acetylcholine during the breathing of 4 - 5% oxygen with 96 - 95% nitrogen while the oxygen content of the blood fell to 86 - 68% with hypocapnia caused a much greater fall of pressure in the greater circula-

tion and a greater increase in breathing and heart rates than occurred when air was breathed; in the latter case there was a marked depressor response in the vessels of the lesser circulation (Fig. 1, B). Under these conditions, the injection of acetylcholine caused a fall in the systolic pressure of the greater circulation of on average 20 - 25 mm mercury, while the diastolic pressure fell by 30 - 35 mm. In the lesser circulation, in 10 cases the pressure fell on average by 4 - 6 mm, though in two cases there was an increase of 2 - 4 mm. The number of respiratory movements increased on average by 15 - 20 per minute, and the heartbeat by 30 - 35 per minute.

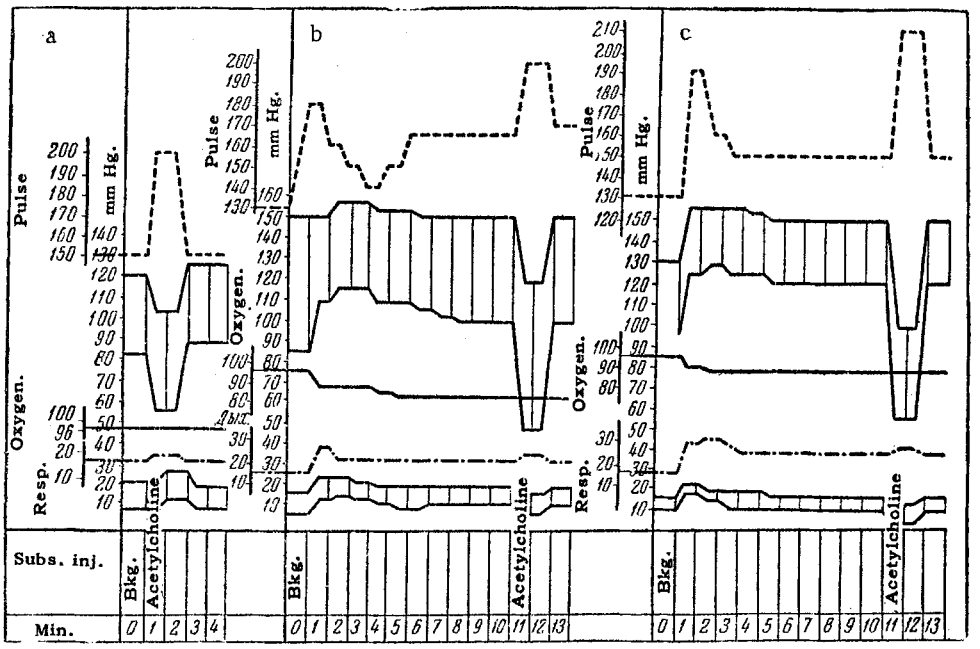

Fig. 1. Change of respiration, heartbeat, and blood pressure in the greater and lesser circulations during the injection of 10 μg of acetylcholine. A) Injection of acetylcholine during air breathing; B) injection of acetylcholine during breathing of 4% oxygen without CO_2; C) injection of acetylcholine during breathing of 4% oxygen with 1.8% CO_2.

When a mixture of 4 - 5% oxygen with nitrogen was breathed, and the hypocapnia was eliminated with small amounts of carbon dioxide, the oxygen content of the arterial blood fell to 78 - 88%; the injection of acetylcholine then caused a more marked pressor response in the greater circulation, and less change in the respiratory and cardiac frequencies than had occurred when the low-oxygen mixture was inhaled during hypocapnia. In the lesser circulation the effect was indefinite (Fig. 1, C). On average, the systolic pressure was reduced by 40 mm mercury, and the diastolic by 50 mm. In six cases, in the lesser circulation the pressure fell by 2 - 10 mm, in four cases it rose by 2 - 8 mm, and in two instances there was no change. The number of respiratory movements per minute increased by 12, and the heart rate by 25 beats per minute.

From what has been said it can be seen that the effect of hypoxia is to increase the tachycardia and the depressor response of the greater circulation induced by acetylcholine. Elimination of the hypocapnia enhanced the acetylcholine-induced depressor response, while the increase in heart rate was reduced.

Adrenalin. The injection of adrenalin while air was breathed always increased the systolic and diastolic pressure in both circulations, reduced the heart and the respiratory rates, and in many cases led to a reduction of 1 - 2% in the oxygenation of the blood (Fig. 2, A). On average, the systolic pressure of the greater circulation rose by 30 - 35 mm, the diastolic rose somewhat less, by 25 mm. In the greater circulation the average maximal rise was 8 - 9 mm mercury, and the minimal 2 - 3 mm. On average the heart rate decreased by 35 - 40 beats per minute, and the respiration rate per minute by 30 - 35.

When adrenalin was injected during the breathing of a mixture poor in oxygen, and while oxygenation of the arterial blood was reduced to 86 - 68%, the pressure in the two circulations was increased very much less; the respiration and heart rates were not as great as when air was breathed (Fig. 2, B). The systolic pressure in the greater circulation rose on average by 15 - 23 mm, and the diastolic pressure by 13 mm. In the lesser circulation the max-

mal pressure rose on average by 5 mm mercury, and the minimal by 2 mm. The respiration rate either remained unchanged or was reduced by 2 - 5 per minute, while the heart rate fell by 20 beats per minute.

After the changeover had been made to breathing air, recovery from the pressor effect occurred in 3-5 minutes, i.e. it occurred at the same rate as the recovery of the oxygenation of the arterial blood.

When adrenalin was injected during the respiration of a mixture poor in oxygen and when the hypocapnia had been eliminated by the addition of small amounts of carbon dioxide, the oxygenation of the arterial blood was reduced to 78 - 86%; there was then always a greater increase of systolic and diastolic pressures in both circulations,

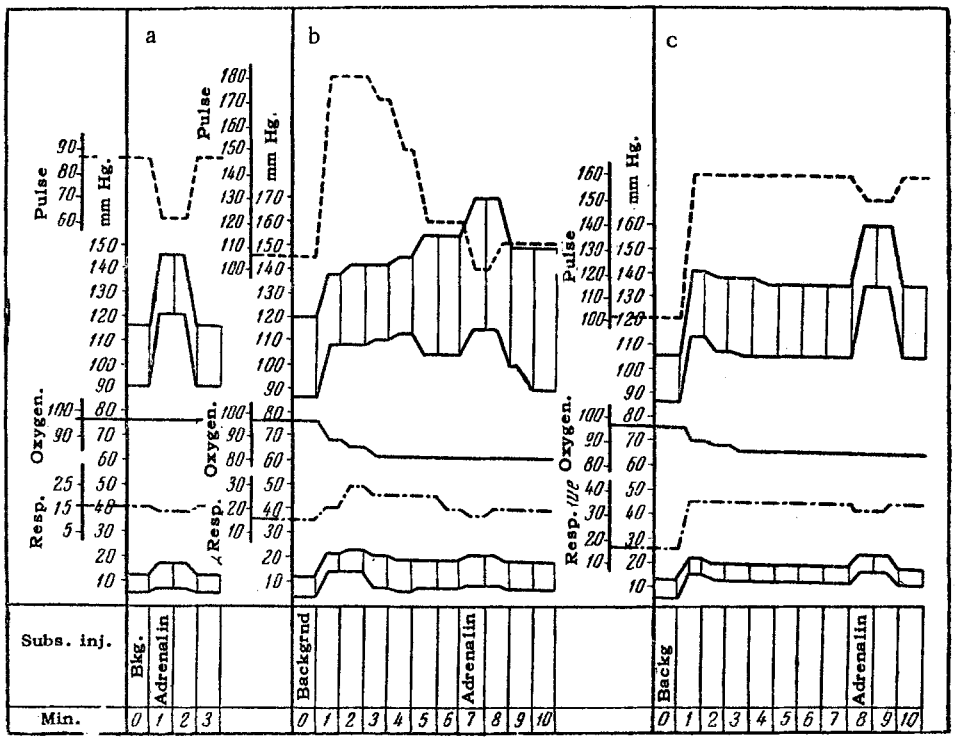

Fig. 2. Change in the respiration and heart rates, and blood pressure in the greater and lesser circulation in response to injection of 0.7 μg /kg of adrenalin. A) Injection of adrenalin during air breathing; B) injection of adrenalin when the animal breathed 4.5% oxygen without CO_2; C) injection of adrenalin during breathing of 4.5% oxygen to which 1.5% CO_2 had been added.

and the respiration rate fell much less than when adrenalin had been injected during hypoxia with hypocapnia. The changes in the heart rate were varied. In many of the experiments the pressure rose to its original value (Fig.2, C). In the greater circulation the systolic pressure rose on average by 27 - 30 mm mercury, and the diastolic by 18 - 20 mm. In the lesser circulation the increase of the maximal pressure was 8 - 9 mm, and the rise of the minimal pressure was 3 - 4 mm. The respiration rate fell by 2 - 8 minute.

Thus the pressor responses to the injection of adrenalin in animals with hypoxia and hypocapnia were 55 - 60% less than in the control animals, and after the hypocapnia had been eliminated the responses increased until they were only 5 - 10% below the values obtained in the control animals.

Serotonin. When serotonin was injected during the breathing of air, the pressure in the greater circulation rose sharply, and then returned within 1 - 2 minutes to its original level. The heart and respiration rates were slowed (Fig. 3, A). Systolic pressure in the greater circulation rose on average by 40 - 45 mm, and the diastolic, somewhat less, by 30 - 35 mm. The maximum pressure in the lesser circulation rose by 12 - 15 mm, and the minimum value either showed no change or an increase of 2 - 3 mm. The respiration rate fell by 2 - 10 per minute, and the heart rate on average by 30 beats per minute.

In hypoxia, just as when adrenalin was injected, there was a reduction of the pressor responses and the extent of the reduction depended upon the degree of hypoxia.

When serotonin was injected during the breathing of a mixture of 8 - 10% oxygen and 90 - 92% nitrogen, the arterial blood oxygenation fell to 90 - 86%, while the systolic pressure in the greater circulation rose on average by 25 mm, and the diastolic pressure by 20 - 22 mm. The maximum pressure in the lesser circulation increased on average by 6 - 8 mm, in three cases the minimal pressure fell by 2 mm, and in six it rose by 2 - 3 mm (Fig. 3, B). The effect of serotonin on respiration and heart rate was variable.

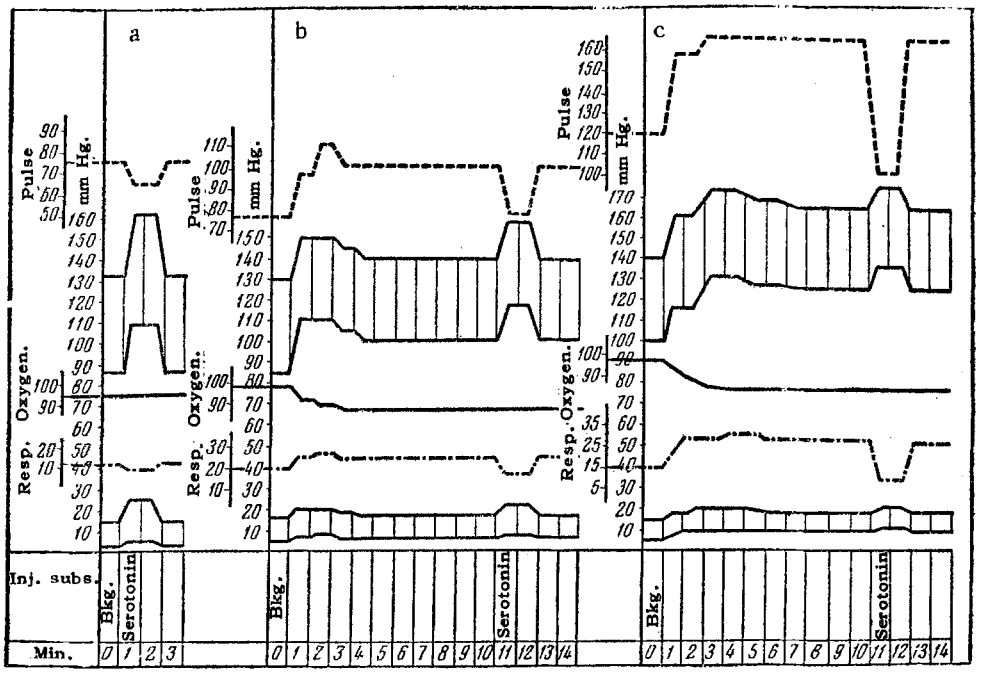

Fig. 3. Change of the respiration rate, cardiac activity, and blood pressure in the greater and lesser circulation induced by the injection of serotonin (10 μg/kg). A) Injection of serotonin while oxygen was breathed; B) injection of serotonin during breathing of a mixture of 8% oxygen without CO_2; C) injection of serotonin while 5.5% oxygen without CO_2 was breathed.

When the animal changed over to breathing air, the recovery from the pressor responses occurred 20 - 30 minutes after recovery of oxygenation.

When serotonin was injected during a more profound hypoxia when there was hypocapnia, the arterial blood oxygenation fell to 68 - 86%, and the pressure in the greater and lesser circulations rose still more sharply than it had done when the hypoxia was only moderate, and returned to the original level after only a few seconds. In most of the experiments respiration and heart rates were greatly slowed (Fig. 3, C).

When the change-over was made to breathing air, recovery from the pressor responses occurred 40 - 50 minutes after recovery of blood oxygenation.

A reduced sensitivity to serotonin during oxygen starvation was therefore demonstrated.

From our observations we may conclude that the reduced sensitivity of the body to adrenalin in hypoxic hypoxia depends not primarily on oxygen lack so much as on the associated hypocapnia. Therefore the concentration of the CO_2 in the body is one of the important factors determining the influence of catecholamines on vascular tone.

SUMMARY

A study was made of the effect produced by 0.7 μg/kg adrenalin, 5 - 10 μg/kg acetylcholine, and 10 - 15 μg/kg serotonin on the greater and lesser circulations in hypoxia accompanied by hypocapnia, and in hypoxia during normal breathing. It was shown that the depressor response in the greater circulation and the tachycardia induced by acetylcholine were increased by hypoxia. Elimination of the hypocapnia enhanced the depressor action induced by acetylcholine, but increased the heart rate less. In oxygen lack, sensitivity to adrenalin and serotonin was reduced. The pressor reactions induced by adrenalin increased during hypoxia, and after elimination of hypocapnia, in many cases the control level was attained.

It appears that the reduction of sensitivity to adrenalin in hypoxia depends mainly not on the hypoxia itself but on the associated hypocapnia.

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