ACTA PHYSIOLOGICA POLONICA
1961, XII, 6, 785

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THE INHIBITORY INFLUENCE OF ANOXIA ON PRESSOR AND CARDIAC EFFECTS OF NORADRENALINE AFTER SYMPATHETIC BLOCKADE *

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Anoxia is well known to reduce in dogs and cats the pressor effects of adrenaline, noradrenaline and hordenine (*Hermann* and *Jourdan* 1941; *Grandpierre, Frank* and *Lemaire* 1943, 1949; *Binet* and *Burstein* 1949; *Frank, Grandpierre, Arnould* and *Lamarche* 1950; *Grandpierre, Frank, Arnould* and *Bouverot* 1954; *Hermann* and *Paulet* 1956). However, the mechanism of this inhibitory influence of anoxia is not clear. It has been claimed by *Hermann* and *Paulet* (1956) to be the result of a decreased reactivity of blood vessels brought about by anoxia. More recently, *Paulet* (1957, 1958) has shown that histotoxic anoxia does not exert in spinal dogs any inhibitory influence on the pressor effects of sympathomimetic amines. The vasoconstrictor effects of these amines in a denervated and perfused limb were not affected by histotoxic anoxia either. The conclusion has been drawn from these experiments that anoxic stimulation of the sympatho-adrenal system, resulting in a powerful and profuse vasoconstriction, might be responsible for a decreased effectiveness of exogenic pressor amines. On the contrary, the author's own experiments (*Litwin*, 1959) have demonstrated that the inhibitory influence of asphyxia on pressor effects of splanchnic nerve stimulation persists in cats after transection of the spinal cord and bilateral adrenalectomy.

As it was difficult to solve this controversy on the basis of the experimental evidence actually available, further investigations seemed to be necessary in order to clarify the mechanism of the inhibitory influence of

* The experiments have been performed during the tenure of the Rockefeller Foundation Fellowship, in the Department of Pharmacology, University of Pennsylvania Schools of Medicine, Philadelphia, Pa, USA.

anoxia on the pressor effects of sympathomimetic amines. The experiments that are reported below have been performed in an attempt to contribute to the elucidation of this mechanism.

METHODS

The experiments were carried out on 10 mongrel dogs, weighing 10 to 17 Kg., which were anaesthetized with morphine sulphate (2 mg./Kg. s. c.) and chloralose (70 mg./Kg. i. v.). In all experiments the chest was opened in the left fifth intercostal space and the lungs were ventilated by means of a Starling Ideal Pump. A mixture of 5 per cent oxygen in nitrogen was administered through the pump to produce acute anoxemic anoxia. Manuronate (10 mg./Kg.) or heparin (200 to 400 I. U./Kg.) was injected intravenously as an anticoagulant. A Sanborn Poly Viso was used to record the following: a) aortic blood pressure by a Statham transducer from a catheter inserted via the right femoral artery; b) pulmonary arterial pressure by a second Statham transducer from a catheter inserted via one of the branches of the right pulmonary artery; c) pulmonary venous or left atrial pressure by a third Statham transducer from a catheter inserted via the corresponding pulmonary vein, and d) heart contractile force by a Walton strain- gauge sutured to the myocardium of the left ventricle. Noradrenaline (0.5 to 3 μg./Kg.) and adrenaline (1 to 3 μg./Kg.) were injected intravenously. In all experiments bilateral vagotomy was carried out in the neck. Bilateral adrenalectomy was accomplished by a transabdominal approach. Adrenergic nerve endings were blocked by means of a sympatholytic agent — bretylium bromide, administered intravenously in doses of 5 to 10 mg./Kg.

RESULTS

Sympatho-adrenal system intact. In the first series of experiments the influence of acute anoxemic anoxia on the pressor and cardiac effects of noradrenaline was studied in 5 dogs with the sympatho-adrenal system intact.

The inhalation of 5 per cent oxygen, applied over a period of 8 to 10 min., caused always a marked rise of the systemic arterial blood pressure, as well as the pulmonary arterial pressure. The heart contractile force increased in the beginning of anoxia and then gradually diminished.

The experiments have shown that the pressor and positive inotropic effects of noradrenaline (0.5 to 3 μg./Kg.) diminish progressively under the influence of acute anoxemic anoxia. The inhibitory influence of anoxia on these effects became apparent after 2 min. usually and reached its maximum after 4 to 5 min. of the inhalation of 5 per cent oxygen. At this moment pressor effects of noradrenaline were on the average reduced to as little as 20 per cent of their initial values. They remained maximally reduced up to the end of anoxia. In some instances they were almost completely abolished.

During the period of reoxygenation of the animal a gradual increase of both pressor and positive inotropic effects of noradrenaline was observed. They reached their initial values 5 to 15 min. after the reoxygenation was initiated.

Fig. 1 presents in form of a diagram the average values obtained in this series of experiments.

A typical record, representing this experimental series, is shown in fig. 2. Inhalation of 5 per cent oxygen was applied over a period of 8 min.

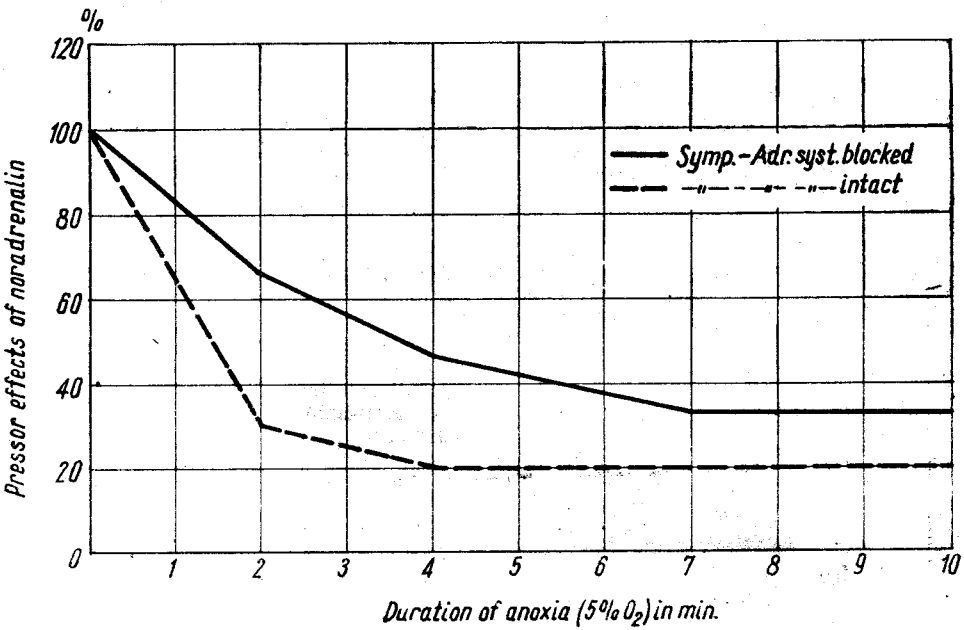

Fig. 1. Comparison of the inhibitory influence of acute anoxemic anoxia on pressor effects of noradrenaline in intact dogs and dogs with the sympatho-adrenal system eliminated.

to produce acute anoxemic anoxia. After 3 min. of inhalation both pressor and positive inotropic effects of noradrenaline (3 μg./Kg.) decreased consideraby and after 6 min. pressor response to this amine was almost completely abolished, the positive inotropic effect being very markedly reduced. The rises of the pulmonary arterial pressure, elicited by noradrenaline, were also obviously attenuated under the influence of anoxia. After the reoxygenation of the animal was initiated, the pressor and positive inotropic effects of noradrenaline began to increase gradually, reaching their initial values after 6 min.

The pressor and cardiac effects of small doses of adrenaline (1 to 3 μg./Kg.) were also observed to decrease considerably under the influence of acute anoxemic anoxia.

Sympatho-adrenal system eliminated. In the second series of experiments the influence of acute anoxemic anoxia on the pressor and cardiac effects of noradrenaline was investigated in 5 dogs in which the sympatho-adrenal system was eliminated. This was achieved by means of administering bretylium bromide and surgical removal of both adrenal glands.

The inhalation of 5 per cent oxygen, continued over a period of 10 min., always caused in these animals a marked lowering of the systemic blood pressure and a decrease of the heart contractile force, which never were preceded by an initial rise, normally appearing in intact animals.

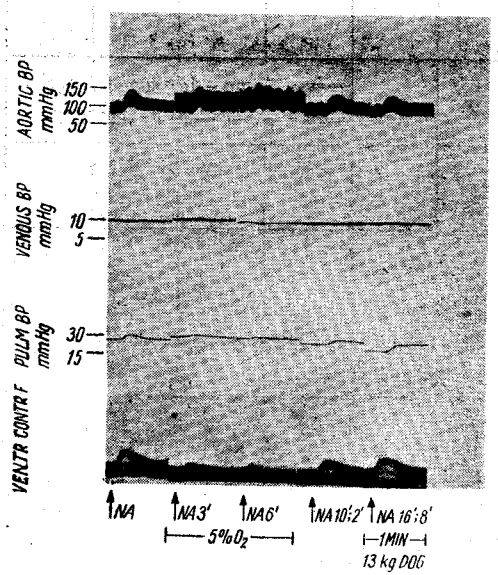

Fig. 2. Inhibition of pressor and cardiac effects of noradrenaline by acute anoxemic anoxia in an intact dog. NA — intravenous injection of noradrenaline (3 μg./Kg.). The first figures at „NA" denote time since the beginning of the inhalation of 5 per cent oxygen, the second ones — time since the beginning of reoxygenation.

It was established in these experiments that the pressor and positive inotropic effects of noradrenaline (0.5 to 3 μg./Kg.) decrease gradually under the influence of acute anoxemic anoxia. The progress of the inhibitory influence of anoxia, however, was visibly slower as compared with animals in which the sympatho-adrenal system was left intact. This was proved by the fact that the effects of noradrenaline reached their minimal values only after 7 to 8 min. of inhalation of 5 per cent oxygen. At this time, however, the per cent decrease of these effects was approximately of the same order of magnitude as in intact animals. The pressor responses to noradrenaline were then reduced on the average to as little as 33 per cent of their control values, remaining at this minimal level up to the end of anoxia.

After readmission of normal air a gradual increase of both pressor and positive inotropic effects was observed. They reached their initial values 5 to 15 min. after the reoxygenation was started.

Fig. 1 presents diagrammatically the average values obtained in this series of experiments. It clearly demonstrates the fact, mentioned above, that although the elimination of the sympatho-adrenal system brought about an evident retardation of the progress of the inhibitory influence of anoxia on pressor effects of noradrenaline, the maximal reduction of these effects was more or less the same both in animals with the sympatho-adrenal system intact and eliminated.

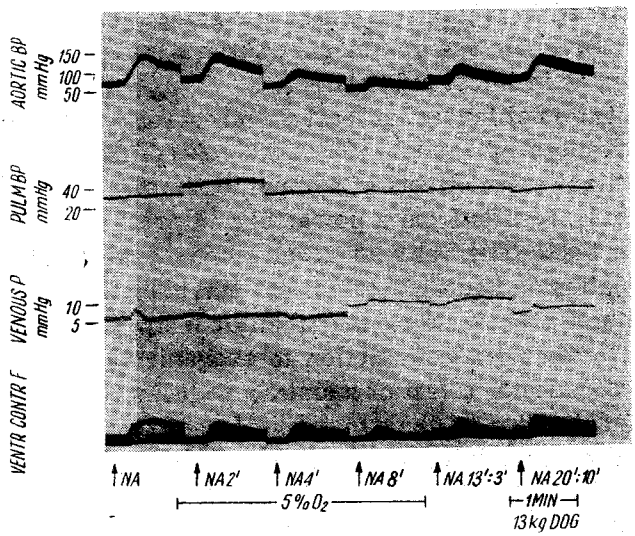

Fig. 3. Inhibition of pressor and cardiac effects of noradrenaline by acute anoxemic anoxia in a dog with the sympatho-adrenal system eliminated.
NA — intravenous injection of noradrenaline (1.5 μg./Kg.). The first figures at „Na" denote time since the beginning of the inhalation of 5 per cent oxygen, the second ones — time since the beginning of reoxygenation.

Fig. 3 shows a typical record obtained in one of the experiments reported above. Inhalation of 5 per cent oxygen, applied over a period of 10 min., resulted in a gradual decrease of both pressor and positive inotropic effects of noradrenaline (1.5 μg./Kg.). The maximum of the inhibition was observed after 8 min. of anoxia. The pressor response to adrenaline was at this moment reduced to 20 per cent of its initial value. After the reoxygenation of the animal was started the pressor and positive inotropic effects of noradrenaline began to increase progressively and reached their initial values after 10 min.

The pressor and cardiac effects of small doses of adrenaline (1 to

3 μg./Kg.) were also observed to diminish markedly under the influence of acute anoxemic anoxia in the animals with the sympatho-adrenal system eliminated.

DISCUSSION

The experimental evidence, presented in this report, indicates that the specific elimination of the sympatho-adrenal system does not abolish the inhibitory influence of acute anoxemic anoxia on the pressor and cardiac effects of small doses of noradrenaline. The progress of the inhibition is evidently retarded in animals in which the sympatho-adrenal system was excluded, however, its maximum shows the same order of magnitude, approximetely, as in intact animals.

These results do not favour, at least with regard to anoxemic anoxia, the hypothesis advanced by *Paulet* (1957, 1958). According to this author, the reduction of the pressor effects of sympathomimetic amines, produced by histotoxic anoxia, results from a powerful and profuse vasoconstrictor action of anoxia itself. The vascular areas responsible for pressor action of both noradrenaline and adrenaline exhibit maximal vasoconstriction in the state of profound anoxia. Being maximally constricted, they are not able to react with further vasoconstriction to exogenic sympathomimetic amines. The vasoconstrictor effect of anoxia is well known to depend entirely on an intense activation of the sympathetic vasoconstrictor fibres and the secretion of adrenal medullary hormones, initiated mainly by the stimulation of chemoreceptors of carotid and aortic bodies.

If the hypothesis proposed by Paulet held true for all types of anoxia, the elimination of the sympatho-adrenal system would thus abolish also the inhibitory influence of anoxemic anoxia on the pressor and cardiac effects of exogenic sympathomimetic amines. As this is not the case, the conclusion seems justified that powerful and profuse vasoconstriction brought about by the activation of the sympatho-adrenal system cannot be regarded as a main factor responsible for the anoxic reduction of the effects of exogenic noradrenaline and adrenaline. This activation, however, may play a contributory role in the initial phase of anoxemic anoxia. This would account for a more rapid progress of the inihibitory influence of anoxemic anoxia on the effects of exogenic noradrenaline and adrenaline in animals in which the sympatho-adrenal system was left intact.

The apparent discrepancy existing between the results of *Paulet* (1957, 1958) and those described in the present study can hardly be explained. It is the author's opinion that one factor must be taken into consideration when analyzing this question. It cannot be excluded that the effects of

anoxemic anoxia may in some way deviate from the effects of cyanide intoxication (histotoxic anoxia), investigated by *Paulet*. It seems possible that this may account for a good deal of difference.

On the basis of the experiments, reported in this paper, following mechanisms for the inhibitory influence of anoxemic anoxia on the pressor and cardiac effects of sympathomimetic amines seem probable: 1) decreased reactivity of the cardiovascular system to the action of these amines, elicited by oxygen deficiency and/or accumulation in the organism of the metabolic products of anoxia, and 2) increased effectiveness of nervous compensatory adjustments, participating in the regulation of the cardiovascular functions, brought about by anoxia. As all adrenergic nervous mechanisms were blocked and both vagus nerves sectioned, cholinergic vasodilator efferents only were left intact in animals used in the author's experiments. However, the participation of cholinergic vasodilator mechanisms in the phenomenon in question can hardly be conceived from theoretical standpoint, since it is known that these mechanisms do not play any major role in the regulation of systemic blood pressure. This conclusion is in agreement with the results of the author's earlier experiments which have demonstrated in cats a strong inhibitory influence of asphyxia on depressor effects of a number of hypotensive agents, including acetylcholine (*Litwin*, 1958 a, b; *Litwin* and *Janczewska*, 1959 a, b). The assumption seems, therefore, more likely that the reduction of pressor as well as cardiac effects of sympathomimetic amines, due to anoxemic anoxia, results from the decreased responsiveness of the cardiovascular system.

Summary

1. Acute anoxemic anoxia, produced by means of the inhalation of 5 per cent oxygen in nitrogen, causes in anaesthetized dogs a considerable reduction of pressor and cardiac effects of noradrenaline (0.5 to 3 μg./Kg. i. v.). The maximal reduction of these effects commences usually 4 to 5 min. after the initiation of anoxia.

2. Elimination of the sympatho-adrenal system by means of bretylium bromide (5 to 10 mg./Kg. i. v.) and bilateral adrenalectomy does not abolish the inhibitory influence of acute anoxemic anoxia on pressor and cardiac effects of noradrenaline. The progress of the inhibition is evidently less rapid than in intact animals, its maximum, however, reaches the same order of magnitude approximately.

3. Profuse and powerful vasoconstriction, caused by anoxic activation of the sympatho-adrenal system, cannot be considered to be the main factor responsible for the reduction of the pressor effects of noradrenaline consequent to anoxemic anoxia. It may, however, contribute to this reduction in the initial phase of anoxia, thus accounting for the more rapid progress of the phenomenon in animals in which the sympatho-adrenal system is left intact.

4. The mechanism underlying the inhibitory influence of acute anoxemic anoxia on pressor and cardiac effects of sympathomimetic amines is discussed.

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HAMUJĄCY WPŁYW ANOKSJI NA PRESYJNE I SERCOWE EFEKTY NORADRENALINY W WARUNKACH BLOKADY UKŁADU WSPÓŁCZULNEGO

Streszczenie

Doświadczenia były przeprowadzone na 10 psach w narkozie morfinowo-chloralozowej. We wszystkich doświadczeniach otwierana była klatka piersiowa i stosowane sztuczne oddychanie. Ostra anoksja anoksemiczna wywoływana była przez inhalację 5% tlenu w azocie. Noradrenalina stosowana była dożylnie w dawkach 0.5—3 μg/kg. U wszystkich zwierząt wykonywana była obustronna wagotomia.

Doświadczenia wykazały, że ostra anoksja anoksemiczna powoduje u psów znaczne zmniejszenie się presyjnych i sercowych efektów noradrenaliny. Maksimum tego zmniejszenia występowało zazwyczaj po 4—5 min. od chwili rozpoczęcia inhalacji 5% tlenu w azocie. Wyłączenie układu współczulno- nadnerczowego przy pomocy bromku bretylium (5—10 mg/kg) i obustronnej adrenalektomii nie znosi hamującego wpływu anoksji na presyjne i sercowe efekty noradrenaliny. Narasta on wprawdzie wyraźnie wolniej, osiąga jednakże w końcu ten sam rząd wielkości co u zwierząt normalnych. Wynika stąd, że rozległe zwężenie naczyń krwionośnych wywoływane przez anoksję na drodze pobudzenia układu współczulno-nadnerczowego, nie może być czynnikiem głównie odpowiedzialnym za zmniejszenie się efektów egzogennej noradrenaliny pod wpływem anoksji. Mechanizm hamującego wpływu anoksji na presyjne i sercowe efekty noradrenaliny jest dyskutowany.

REFERENCES

1. *Binet L., Burstein M.:* C. R. Soc. Biol., 1949, 143, 1545.
2. *Frank C., Grandpierre R., Arnould P., Lamarche M.:* C. R. Soc. Biol. 1950, 144, 1687.
3. *Grandpierre R., Frank C., Arnould P., Bouverot P.:* C. R. Soc. Biol. 1954, 148, 1470.
4. *Grandpierre R., Frank C., Lemaire R.:* 1943, cit. after 7.
5. *Grandpierre R., Frank C., Lemaire R.:* J. de Physiol. 1949, 41, 189A.
6. *Hermann H., Jourdan F.:* 1941, cit. after 7.
7. *Hermann H., Paulet G.:* C. R. Soc. Biol. 1956, 150, 672.
8. *Litwin J.:* Bull. de l'Acad. Pol. des Sci. Cl. VI, 1958a, 6, 125.
9. *Litwin J.:* Acta Physiol. Pol. 1958b, 9, 411.
10. *Litwin J., Janczewska H.:* Bull. de l'Acad. Polon. des Sci. Cl. VI, 1959, 7, 155.
11. *Litwin J., Janczewska H.:* Acta Physiol. Pol., 1959b, 10, 297.
12. *Litwin J.:* Bull. de l'Acad. Polon. des Sci. Cl. VI, 1959c, 7, 277.
13. *Paulet G.:* J. de Physiol. 1957, 49, 339.
14. *Paulet G.:* J. de Physiol. 1958, 50, 31.

Otrzymano: 4. 5. 1961.

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