ON THE RELATION OF CHEMORECEPTOR STIMULATION TO EPINEPHRINE SECRETION IN ANOXEMIA

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Epinephrine secretion in anoxemia has been considered to play an emergency role only in severe cases. A significant increase in blood epinephrine level does not occur until the arterial O₂ saturation falls below 50% (Ludeman et al.). Under such severe anoxic conditions the increased secretion of epinephrine may well contribute to the rise in cardiac output, but not in more moderate hypoxia (Korner). However, as will be demonstrated here, epinephrine secretion in anoxemia depends markedly upon the type of anoxemia induced. The hyperglycemic response to epinephrine secretion is far more marked in case of anemic type of anoxemia due to CO inhalation than in case of hypoxic type of O₂ lack. In this regard it should be remembered that in the former case chemoreceptor stimulation is absent so long as O₂ partial pressure remains normal (Comroe & Schmidt). The generally accepted assumption that reflex chemoreceptor drive is one of the potent mechanisms of stimulating the epinephrine secretion in asphyxia (Euler), seems, therefore, to be incompatible with this observation. Thus it was tried to determine the role played by the chemoreceptors in epinephrine secretion in anoxemia.

METHODS

Rabbits weighing about 2.5 kg were trained to bear a small gas mask covering the nose and the mouth in a loosely restraining box, so that the “restraint” hypothermia which could also induce hyperglycemia was avoided. Experiments were done after 18 hours fasting without anesthesia. O₂-N₂ mixture or CO containing air was delivered through the gas mask from a Douglas bag pressed by a constant weight. CO was prepared by dropping concentrated oxalic acid into concentrated arsenic-free sulphric acid. The gas was passed first through a strong solution of NaOH, then through a distilled water, and was stored in a spirometer over water.

Blood samples were taken from the denervated ear vein well dilated by heating. The blood sugar was determined by the Somogyi method and the blood gas was analysed by a microgasometer after Natelson. The percentage of carboxyhaemoglobin was calculated from the reduction of the O₂ content.

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In case of blood pressure measurement it was recorded by a mercury manometer through carotid canulation. The respiratory curve was simultaneously registered by a tambour attached to a side-tube of the outlet of the gas mask. When ear temperature was measured a thermocouple was plastered to the ear near to the central artery. In this case the denervation of ear vessels was avoided.

RESULTS

I. The Hyperglycemic Response in Anoxemia as the Manifestation of Epinephrine Secretion. As is shown in Fig. 1 the hyperglycemic response on inhalation of CO could be almost completely inhibited either by bilateral adrenalectomy or splanchnicotomy. This was also the case with inhalation of O₂-N₂ mixtures of low oxygen content. Therefore, the hyperglycemic response in anoxemia could be used as an index of epinephrine secretion induced centrally. Approximate rate of secretion of epinephrine could be estimated from the magnitude of the hyperglycemic response. Fig. 2 represents the relation of the magnitude of hyperglycemia to the rate of epinephrine infusion for 30 minutes. In case of inhalation of 0.4% CO for 45 minutes the blood sugar rise which started after latency of about 15 minutes corresponded to epinephrine infusion at a rate of 0.8-1.0 μg/kg/min.

The secretion of epinephrine on inhalation of CO, however, did not only depend upon the amount of carboxyhaemoglobin formed, but also upon the rate

![Fig. 1. Hyperglycemic response on inhalation of CO. The blood sugar level begins to rise after a definite latency. Both adrenalectomy and splanchnicotomy abolishes the response.](image-url)
FIG. 2. Relation of the magnitude of hyperglycemia to the rate of epinephrine infusion.
Duration of infusion: 30 minutes.

FIG. 3. CO-hyperglycemia in relation to the rapidity with which the same percentage of CO-Hb (40%) was attained.
of its formation. As shown in Fig. 3 slow attainment to 40% carboxyhaemoglobin content with long continued inhalation of low concentrated CO could not induce hyperglycemia. Therefore, the epinephrine secretion depends upon the rapidity of the development of the CO-anoxemia rather than its degree. This fact also clearly indicates that CO itself does not exert any specific effect in inducing the epinephrine secretion.

II. Comparison of the Hyperglycemic Response in CO-Anoxemia and Hypoxic Anoxemia. The hyperglycemic response in CO-anoxemia and hypoxic anoxemia were compared in relation to arterial O₂ saturation (Fig. 4(A)). In the abscissa the O₂ content at the termination of the inhalation (60 minutes) was represented as the saturation degree, irrespective of the oxygen partial pressure. There exists a quite striking difference. In the same saturation degree the hyperglycemic response indicating the epinephrine secretion was far marked in case of CO-anoxemia than in case of hypoxic anoxemia. It is quite remarkable, if we consider the circumstances that in case of CO-anoxemia the partial pressure of O₂ remained unaltered and, therefore, the anoxic effect of the same oxygen content might be expected to be less than that due to hypoxic anoxemia. It seems to be true that some other factors other than the anoxemia itself plays a dominant role in initiating the epinephrine secretion in anoxemia. In this respect the absence of chemoreceptor stimulation in CO-anoxemia seems to deserve attention.

III. Effect of Carotid Bodies Extirpation upon the Hyperglycemic Response in Hypoxic Anoxemia. In order to verify the above assumption, experiments were
made on the significance of the stimulation of the chemoreceptors in case of hypoxic anoxemia. As is shown in Fig. 4(B) the hyperglycemic response to the same reduction of arterial saturation was found to be markedly intensified after bilateral carotid bodies extirpation. Hereby, in order to attain the same level of arterial O$_2$ saturation it was naturally necessary to use far higher O$_2$ concentration for inhalation in the carotid bodies extirpated animals than that used for intact animals. At any rate, it is sure that the stimulation of chemoreceptors in hypoxic anoxemia exerted an inhibitory effect upon the epinephrine secretion in anoxemia, contrary to a current assumption that reflex chemoreceptor drive would be one of the potent mechanisms of stimulating the epinephrine secretion in asphyxia$^4$.

IV. Relation of Chemoreceptor Stimulation to Epinephrine Secretion in Anoxemia. It should be considered that the ablation of carotid bodies weakens the hyperventilation in hypoxic anoxemia, causing an increase in the depth of anoxemia and less acapnia. However, the absence of hypocapnia could not be the main cause of the intensification of the epinephrine secretion after carotid bodies extirpation, since addition of CO$_2$ to O$_2$-N$_2$ mixtures in concentration up to 5.0% could not materially influence the hyperglycemic response. This result is somewhat contrary to that of GELLHORN and PACKER$^7$ with which it will be discussed later.

There remains to be considered the anoxic hypotension in the absence of carotid bodies. BOUCKAERT et al.$^8$) have already shown that in dogs deprived of chemoreceptors the anoxic hypotension was markedly intensified. However, the effect upon the blood pressure was not compared at the same O$_2$ saturation and, moreover, the experimental conditions were drastic. For excluding chemoreceptors, beside extirpation of both carotid bodies both vagi were cut and all experiments were done under chloralose anesthesia. In the rabbits here used only extirpation of carotid bodies was sufficient in suppressing the anoxic hyperventilation and its effect upon the blood pressure could be observed without anesthesia and fixation. In Fig. 5(a, b) the results of inhalation of 10% O$_2$ in an carotid bodies extirpated animal were given in comparison with those of inhalation of 5% O$_2$ in an intact animal. In both cases, although the arterial O$_2$ saturation dropped to about 60% at the end of the inhalation for 30 minutes, anoxic hypotension could only be observed in the carotid bodies extirpated animal. Thereby, on close examining the blood pressure curve (b) it will be noticed that it began to drop within a few minutes when respiration slowed down. However, the drop was prevented at about 60 mm Hg with simultaneous increase in pulse pressure and respiration rate. This adaptation might be due to enhanced epinephrine secretion and not due to the activation of the sympathetic nervous system. As shown in Fig. 6(B) just corresponding to the onset of this adaption a marked vasodilatation of the ear vessels was observed. This sort of vasodilatation always occurred when anoxic hyperglycemia appeared and was absent after adrenalectomy (Fig. 6(A)). It is also characterized by its abrupt onset and
accompanied by some discomfort. It seems to be due to the inhibition of vaso-constrictor tone by intense epinephrine secretion\(^9\).

As shown in Fig. 5(c) similar changes in blood pressure and respiration to those of the carotid bodies extirpated animal above mentioned could be observed in intact animal on inhalation of CO. The recovery of blood pressure with simultaneous increase in the pulse pressure occurred also at about 60 mm Hg. This
was about 15 minutes after the beginning of inhalation of 0.4% CO and corresponded to the latency of the blood sugar rise and the vasodilation mentioned above.

Thus it may be concluded that the epinephrine secretion in anoxemia is mainly conditioned by the anoxemic hypotension rather than the anoxemia itself, and that the absence of chemoreceptor stimuli precipitated the anoxic hypotension and induced intense epinephrine secretion. In passing it may be added here that the hypocapnia in case of inhalation of 6% O2 in intact animals does not concern with the prevention of the anoxemic hypotension, since addition of CO2 in concentration of 5% did not induce hypotension. This might also explain the previously mentioned results that the effect of addition of CO2 in increasing the hyperglycemic response was only slight.

**DISCUSSION**

It has been concluded that a marked hyperglycemia due to epinephrine secretion in anoxemia could only be observed when carotid body stimulation was absent. This is contrary to the view generally held that chemoreceptor stimulation might induce reflex epinephrine secretion in asphyxia\(^4\). Such a view has been deduced from the observation of adreno-medullary secretion in case of carotids occlusion in which the pressor response has been interpreted by activation

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**Fig. 6.** Changes in ear temperature.

A. CO inhalation

B. low O2 inhalation
of the stretch receptor associated with stimulation of the carotid bodies by hypoxia\textsuperscript{10}). The condition of epinephrine secretion in this case, even if it really occurs\textsuperscript{11}), might be complicated by the sudden drop of the blood supply to the brain. In this regards it may be added here that in rabbits here used adrenal secretion of norepinephrine which fails to be reflected in the hyperglycemic response has been assumed to be negligible\textsuperscript{12}).

The inhibition of epinephrine secretion by carotid body stimulation has been attributed to the prevention of anoxic hypotension and the critical mean arterial pressure for the initiation of intense epinephrine secretion in anoxemia was estimated to be about 60 mm Hg in rabbits. It has been already noticed by several workers that animals were in approaching cardiovascular failure when intense epinephrine secretion was observed\textsuperscript{13}). However, at the time of commencement of epinephrine secretion noticed on the blood pressure curve no anoxic sign could be observed both on EEG and ECG. The details will be published in another paper. In cases of haemorrhagic shock WALKER et al.\textsuperscript{14}) have recently suggested that the adrenal medullary secretion might be governed by the blood volume changes rather than alteration in arterial blood pressure. The dominant role played by the arterial pressure here observed might be understood by the circumstances that in the brain stem the intrinsic regulation of circulation against anoxemia is well developed (SCHMIDT\textsuperscript{15}) and unless arterial hypotension disturbs this, no anoxic stimulation of the epinephrine secreting center might take place. The fact that the epinephrine secretion in case of CO-anoxemia depended upon the rapidity of the development of the anoxemia rather than its degree might be due to this intrinsic regulation which prevents anoxic hypotension when anoxemia proceeds slowly.

Concerning the blood sugar response to hypoxemia and/or hypocapnia experiments were done recently by BIDDUPH and VON FOSSAN\textsuperscript{13}) on dogs. In this animal the hyperglycemia was slight and the results were different in relation to the duration of the exposure. At any rate for hypercapnic stimulation of the epinephrine secreting center a very high pCO\textsubscript{2} is necessary as will be noticed in case of diffusion respiration by MILLER\textsuperscript{16}). The conclusion of GELLHORN and PACKER\textsuperscript{7}) that the addition of 5.4% CO\textsubscript{2} to 7% O\textsubscript{2} for inhalation markedly intensified the hyperglycemic response due to the latter in rabbits is not a constant finding, since on close examination of their data no intensification was observed in 4 out of 18 cases. Moreover, the maximum rise of the blood sugar level was attained at 15 minutes and the level declined thereafter on continuation of the inhalation. This is difficult to understand under well controlled experimental condition.

**SUMMARY**

It has been demonstrated that the hyperglycemic response due to epinephrine
secretion in anoxemia depends markedly upon the type of anoxemia induced. CO-anoxemia, a special type of anemic anoxemia, induced a marked one, whereas hypoxic anoxemia of considerable O₂ lack provoked only a slight one. The absence of chemoreceptor stimulation in the former might be responsible for this difference, since after extirpation of carotid bodies a marked hyperglycemic response was also observed in the latter case. It was concluded that the epinephrine secretion in anoxemia is conditioned by the anoxic hypotension which is prevented by chemoreceptor stimulation, rather than the anoxemia itself.

REFERENCES