THE MECHANISM OF THE REFLEX APNEA CAUSED BY NICOTINE ; THE LUNG PERFUSION'S METHOD IN DOGS.

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It has been reported that the apnea caused by nicotine may be due to the reflex from the receptors in the lungs and the afferent fiber pass through the vagus nerves (Takasaki, 1956., Takasaki et al. 1959 a, b).

On the other hand, it has been well known that nicotine has a marked effect on the respiratory center and there is no evidence that the nicotine apnea is not connected with its effect on it also.

This experiment was attempted to confirm the following two points:

- 1) This nicotine apnea has no connection with the respiratory center directly using the perfused isolated head technique.
- 2) The receptors responsible for the nicotine apnea are in the lungs using the lung perfusion's method.

METHODS

Dogs were anesthetized with 1.0g/kg of urethane and 3.0mg/kg of morphine and used in this experiment. Heparine in doses of 3-5mg/kg were given intravenously in all animals.

The perfused isolated head technique of J. F. and C. Heymans was performed. In the recipient dog, both carotid sinus nerves were denervated to prevent the influences of these reflexes.

Respiratory movement of the recipient and donor dog was recorded through the tracheal cannula and the blood pressure was also recorded from the femoral artery of both dogs.

Nicotine was rapidly administered into the right ventricle of the heart in the recipient dog or into the left cannula connecting the carotid artery of both dogs.

The perfused isolated lung technique was shown in Fig. 1. The chest of the recipient dog was opened under the artificial respiration and the left main pulmonary artery and veins were isolated. The left pulmonary artery of the recipient dog was connected with the right carotid artery of the donor dog and the left pulmonary veins of the recipient dog (about three main branches) with the right femoral vein of the donor dog, respectively.

Nicotine was rapidly administered into the side tube of the pulmonary arterial cannula (C).

Blood pressure was measured from the femoral artery of both dogs.

The respiratory movement of the donor dog was recorded through the tracheal

Fig. 1. Schema of the perfused lung.

- A : Left pulmonal artery
- B : Left pulmonal vein
- C : Side tube of pulmonal arterial cannula for injection
- D : Cannula of pulmonal artery
- E : Cannula of pulmonal vein

cannula. The respiratory movement of the recipient dog under the artificial respiration was recorded as follows: The respiratory movement of the abdominal wall, independent from the rhythm of the artificial respiration, occurred when the rate and volume of the respiratory pump were regulated adequately. This movement of the abdominal wall was recorded by the receptor-tambour.

RESULTS

1) *The isolated head perfusion*

An injection of nicotine, in doses of 0.1-0.2mg/kg into the vein or the right ventricle of the recipient dog, produced the fall of blood pressure and heart rate and the reflex apnea, which was followed by the secondary rise and the respiratory acceleration in rate and depth (Fig. 2A).

After the injection of nicotine in dose of 0.02mg/kg into the carotid cannula, the apnea could never be observed and only a slight respiratory stimulation was observed.

After the vagotomy not only the circulatory depressor response but also the apnea caused by intravenously injected nicotine, could be no longer observed, though the secondary rise of blood pressure and the respiratory acceleration remained (Fig. 2B).

Fig. 2. The isolated head perfusion.

RR : Respiration of the recipient dog

DR : Respiration of the donor dog

RB : Blood pressure from the femoral artery of the recipient dog

DB : Blood pressure from the femoral artery of the donor dog

Time intervals : 10 seconds

A : Nicotine 0.1mg/kg into the right ventricle of the recipient dog

B : Nicotine 0.1mg/kg into the right ventricle of the recipient dog after bilateral vagotomy

Fig. 3. The isolated lung perfusion.

Nicotine 1.0mg/kg into the cannula of pulmonary artery. Respiration of the recipient dog (RR) stopped for about 20 seconds and blood pressure (RB) fell about 30mmHg. Respiration of the donor dog (DR) stopped for about 20 seconds at 20 seconds after the injection and the fall of blood pressure and heart rate occurred simultaneously.

2) *The isolated lung perfusion*

The nicotine in doses of 0.2-0.5mg/kg administered into the inflowing cannula of the pulmonal artery of the recipient dog immediately produced the expiratory apnea or "the expiratory effect" for 10-20 seconds and a fall of blood pressure (10-25mmHg) in the recipient dog. Thereafter, the apnea and the following acceleration of respiration and the circulatory effects were also observed in the donor dog. These effects were similar to those caused by intravenously injected nicotine in a normal dog.

The nicotine in doses of 1mg/kg or more administered into the pulmonal artery of the recipient dog obviously produced the apnea for 10-20 seconds. The fall of blood pressure (about 30mmHg or more) and very slight bradycardia were observed simultaneously (Fig. 3).

DISCUSSION AND CONCLUSION

Evidences presented in the experiment of the isolated perfused head preparation, strongly indicated that the nicotine apnea was not due to the direct effect of the drug on the respiratory center, since the administration in carotid artery never produce the apnea, and the afferent fiber for this reflex passed through the vagus nerves, since the apnea could not be observed after vagotomy.

Aviado et al. (1951), who attempted to confirm the location of the receptor for the veratridine apnea, used the isolated perfused lung preparation with the aid of a perfusion pump.

In our experiment, the donor dog was used instead of the pump. Accordingly, there is an advantage to be able to ascertain whether the perfusion is performed completely or not. As a matter of fact, the apnea and the circulatory response can be observed not only in the recipient but also in the donor dog, when the perfusion is in good condition. The recipient dog is affected by the drug only in the perfused lung, nevertheless, the apnea and fall of blood pressure still occur.

This result shows that the receptors for the apnea are in the lung (between the pulmonal artery bifurcation and the pulmonal vein).

Furthermore, Brodie (horse serum and the electrical stimulation of the pulmonal branches of vagus nerve, 1900), Dawes G. S. (amidine, guanidine, isothiouraea, 1950a, b) and Bagoury (ethylacetoacetate and ethylpropionate, 1941) observed that there is the vagal circulatory reflex originated in the lungs. This reflex has been defined as the "pulmonary depressor chemoreflex" (Dawes et al., 1954). However, there have been a few direct evidences using the isolated perfused lung.

In the present experiment, the fact that the hypotension in the recipient dog was clearly observed, may show the existence of this reflex.

REFERENCES

1. AVIADO, D. M. JR., LI, T. H., KALOW, W., SCHMIDT, C. F., TURNBULL, G. L. & PERKIN, G. W.: Respiratory and circulatory reflexes from the perfused heart and pulmonary circulation of the dog. *Am. J. Physiol.*, 165,261-276, 1951.
2. BAGOURY, M. M. & SAMAAAN, A.: Reflexes of pulmonary origin evoked by the pressure of Ketone bodies in the blood. *J. Egypt. Med. Ass.*, 24, 211-223, 1941.

3. BRODIE, T. G. The immediate action of intravenous injection of blood-serum. *J. Physiol.*, 26, 48-71, 1900.
4. DAWES, G. S. & MOTT, J. C. : Circulatory and respiratory reflexes caused by aromatic guanidines. *Brit. J. Pharmacol.*, 5, 65-76, 1950a.
5. DAWES, G. S. & FASTIER, F. N. Reflex action of some isothiouraea derivatives on circulation and respiration. *Brit. J. Pharmacol.*, 5, 323-334, 1950b.
6. DAWES, G. S. & COMROE, J. H. JR. : Chemoreflexes from the heart and lungs. *Physiol. Rev.*, 34, 167-201, 1954.
7. HEYMANS, J. F. & HEYMANS, C. : Verfahren um den isolierten Hundekopf durch Anastomose mit den Blutkreislauf eines anderen Hundes überlebend zu halten. *Abderhaldens Handb. Biol. Arbeitsmeth.*, 5, 1075-1079, 1926.
8. TAKASAKI, K. : The mechanism of the reflex apnoea caused by nicotine, especially on the species difference between cat and rabbit. *Kurume Med. J.*, 3, 146-159, 1956.
9. TAKASAKI, K., SAKAI, K., MIYAZAKI, N. & NAGASAKI, N. : The mechanism of the reflex apnea caused by nicotine; Influences of intrapericardially injected procaine on the apnea in cats, rabbits and dogs. *Kurume Med. J.*, 6, 104-110, 1959a.
10. TAKASAKI, K., YOKOO, H. & NAGASAKI, N. : The mechanism of the reflex apnea caused by nicotine; Influence of cutting the vagal pulmonal branches and of injection into the pulmonal artery in cats, dogs and rabbits. *Kurume Med. J.*, 6, 152-157, 1959b.