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Responsiveness of the Denervated Adrenal Medulla to Carbaminoylcholine

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In dogs anesthetized with Evipan-sodium, the denervation of the left adrenal gland was performed by cutting the splanchnic nerves about three weeks before and that of the right gland at the time of observation. The venous blood from the right as well as from the left gland was collected through the lumbar route and was analysed for adrenaline by the chemical method of BLOOR and BULLEN. Carbaminoylcholine caused a definite increase in adrenaline secretion of the chronically denervated gland, the rate of increase being almost the same as that of the acutely denervated one. The evidence is presented that the chronic denervation of the adrenal gland does not affect the adrenaline secretory responsiveness to carbaminoylcholine.

The concept of the so-called "law of denervation" introduced by CANNON²⁾ may lead us to suppose an increase in susceptibility of the adrenal medulla caused by chronic denervation. However, WADA⁵⁾ has demonstrated no increase due to chronic denervation in the responsiveness of the adrenal medulla to acetylcholine.

Since previous studies have shown that carbaminoylcholine was capable of considerably increasing the adrenaline secretion of the acutely denervated gland as well as that of the gland with intact innervation,⁶⁾⁷⁾ it is of interest to know the responsiveness of the chronically denervated gland to carbaminoylcholine.

METHODS

Dogs, weighing from 9.7 to 11.5 kg, were used. The left splanchnic nerves were sectioned through the lumbar route under Evipan-sodium anesthesia. About three weeks later the section of the right splanchnic nerves was performed two hours before the onset of observation. On the day of the experiment, the lumbar route preparation of SATAKE et al.⁴⁾ for collecting the adrenal venous blood was made. The adrenal vein was exposed on the left as well as the right side through the lumbar route and a small cannula was inserted into the vein just lateral to the adrenal gland. The femoral artery was connected with the mercury manometer to register the blood pressure. The saphenous vein, in which a small cannula

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was inserted, was used for intravenous injection of chemicals.

After atropinizing the animal, intravenous injections of carbaminoylcholine chloride (Doryl, Merck) in doses of 0.25 mg and 0.4 mg per kg were performed. The adrenal venous blood from the gland of one side was collected before injection of carbaminoylcholine as well as during the first and the second 60-second period after the start of injection. After an interval, atropine was injected again. Then carbaminoylcholine in the same amount was administered, the adrenal venous blood from the gland of the opposite side being collected in the same manner as before. The adrenaline content of the blood samples was estimated colorimetrically by means of the BLOOR and BULLEN method.¹³ Adrenaline (Merck) dissolved in 1/10 N hydrochloric acid solution was taken as the reference standard.

RESULTS

The experiments were performed on dogs, whose left splanchnic nerves were cut about three weeks before and the right ones on the day of experiment. A comparison was made between the responsiveness of the chronically denervated gland to carbaminoylcholine and that of the acutely denervated one. The data are shown in Table 1.

In Dog 1, the left splanchnic nerves were sectioned 20 days before and the right ones 2 hours before observation.

After the injection of carbaminoylcholine in a dose of 0.25 mg per kg, the adrenaline secretion rate of the acutely denervated gland increased. The highest rate, which was measured during the first 60-second period after the start of injection, was 0.12 $\mu\text{g}/\text{kg}/\text{min}$. in contrast to an immeasurably small rate before injection. During the second 60-second period, it was 0.04 μg . Subsequently, the adrenaline secretion rate of the chronically denervated gland following the injection of carbaminoylcholine in the same dose as before was measured. The secretion rate before injection of carbaminoylcholine was 0.02 $\mu\text{g}/\text{kg}/\text{min}$. and following injection it was found to have increased, 0.09 μg and 0.03 $\mu\text{g}/\text{kg}/\text{min}$. being estimated in the first and the second 60-second period, respectively.

In the second place, this dog was given an intravenous injection of carbaminoylcholine in a dose of 0.4 mg per kg. Before the injection, the secretion rate of the acutely denervated gland was 0.02 $\mu\text{g}/\text{kg}/\text{min}$. After injection of carbaminoylcholine, a noticeably increased secretion rate of 0.40 μg was found in the first 60-second period. In the second 60-second period the secretion rate was measured as 0.04 $\mu\text{g}/\text{kg}/\text{min}$. Thereafter, the same dose of carbaminoylcholine was injected again. After carbaminoylcholine injection, the adrenaline secretion rate of the chronically denervated gland increased markedly. It increased from 0.02 μg to 0.32 μg within the first 60-second period after injection. During

TABLE 1.
Augmentation of Adrenaline Secretion Rate Produced by
Carbaminoylcholine in the Chronically Denervated Adrenals

No. of dog	Body weight and Sex	Dose of carbaminoylcholine (mg/kg)	Adrenaline secretion rate ($\mu\text{g}/\text{kg}/\text{min.}$)					
			The acutely denervated gland			The chronically denervated gland		
			Before injection	After injection		Before injection	After injection	
				0"–60"	60"–120"		0"–60"	60"–120"
1	9.8 kg	0.25	*	0.12	0.04	0.02	0.09	0.03
	♂	0.40	0.02	0.40	0.04	0.02	0.32	0.01
2	11.5 kg	0.25	*	0.02	0.03	*	0.01	0.01
	♀	0.40	*	0.17	0.07	0.007	0.20	0.11
3	9.7 kg	0.25	*	0.07	*	*	0.06	*
	♂	0.40	*	0.44	0.04	*	0.38	0.06

* Immeasurably small amount of adrenaline in adrenal venous blood.

the second 60-second period, it was estimated as $0.01 \mu\text{g}$.

In Dog 2, the left splanchnic nerves were sectioned 18 days prior to the experiment, the right ones being cut 2 hours before observation.

The adrenaline secretion rates of the pair of glands before the first and the second carbaminoylcholine injection were immeasurably small. On receiving 0.25 mg carbaminoylcholine per kg, no appreciable increase in the adrenaline secretion of the acutely denervated gland was observed, $0.02 \mu\text{g}$ and $0.03 \mu\text{g}/\text{kg}/\text{min.}$ being measured during the first and the second 60-second period, respectively. The adrenaline secretion rate of the chronically denervated gland did not increase significantly after the injection of carbaminoylcholine in the same dose as before. It was estimated as $0.01 \mu\text{g}/\text{kg}/\text{min.}$

In the case of 0.4 mg carbaminoylcholine administration, the pre-injection rates of the acutely and the chronically denervated glands were immeasurably small and $0.007 \mu\text{g}/\text{kg}/\text{min.}$, respectively. By 0.4 mg carbaminoylcholine injection, the secretion rate of the former was accelerated considerably and reached $0.17 \mu\text{g}/\text{kg}/\text{min.}$ in the first 60-second period. That of the latter also increased markedly as the result of carbaminoylcholine injection, $0.20 \mu\text{g}/\text{kg}/\text{min.}$ being estimated in the first 60-second period.

In Dog 3, the section of the left splanchnic nerves was done 21 days before and that of the right nerves 2 hours before the onset of experiment.

The rate of adrenaline secretion of the acutely denervated gland before carbaminoylcholine injection was too small to be estimated. After 0.25 mg carbaminoylcholine per kg was injected, the secretion rate was slightly above the pre-injection rate, 0.07 $\mu\text{g}/\text{kg}/\text{min.}$ being estimated in the first 60-second period. The secretion rate of the chronically denervated gland increased only slightly after injection of 0.25 mg carbaminoylcholine per kg and was found to be 0.06 $\mu\text{g}/\text{kg}/\text{min.}$ during the first 60-second period.

Before injection of 0.4 mg carbaminoylcholine per kg, the rate of adrenaline secretion of the acutely denervated gland was immeasurably small. The injection of carbaminoylcholine resulted in a considerable increase in the adrenaline secretion rate such as 0.44 $\mu\text{g}/\text{kg}/\text{min.}$, which was found in the first 60-second period. Further, the adrenaline secretion rate of the chronically denervated gland after injection of 0.4 mg carbaminoylcholine per kg was also found to have increased and was estimated as 0.38 $\mu\text{g}/\text{kg}/\text{min.}$ during the first 60-second period after injection.

DISCUSSION

These experimental results demonstrated that the effect of carbaminoylcholine on the adrenaline secretion of the chronically and the acutely denervated glands was almost of the same magnitude. That is, in Dogs 1-3, in which carbaminoylcholine was injected in a dose of 0.4 mg per kg, the secretion rates of the chronically and the acutely denervated glands were 0.17-0.44 μg and 0.20-0.38 $\mu\text{g}/\text{kg}/\text{min.}$, respectively. Calculating the ratio of the latter to the former in each case, it was on the average about 94:100. In cases in which carbaminoylcholine was applied in a dose of 0.25 mg per kg, except Dog 1 which did not respond to 0.25 mg, the mean ratio in each case was calculated as 81:100 on the average.

If the adrenal medulla is sensitized to stimulus after denervation, the chronically denervated gland may secrete with much greater rate than the acutely denervated one. However, this was not the case in our experiments.

The present results are in agreement with the observation of WADA,⁵⁾ who demonstrated that the responsiveness of adrenal medulla to acetylcholine was not sensitized by the chronic section of the secretory nerve fibers. Although he employed almost the same procedure as that of the present investigation, the stimulating agent differed from that of our experiments. In this connection, the earlier observation of PIERCE and GREGERSEN⁸⁾ should be recalled. In a dog's submaxillary gland after the section of the chorda tympani, they demonstrated that the denervated gland gave a greater response to pilocarpine than did the intact one, although the denervated gland showed somewhat decreased sensitiveness

to acetylcholine. Therefore, it is possible that the increase in the responsiveness of the adrenal medulla after the chronic denervation is not elicited by acetylcholine but by carbaminoylcholine. However, no evidence for this presumption has been demonstrated in our experiments.

Thus, it is concluded that the chronic denervation of the adrenal medulla is not followed by an increased sensitiveness to carbaminoylcholine.

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