The Effect of Eserine upon the Accelerated Adrenaline Secretion Caused by KCl.*

By

Tatuzi Suzuki, Susumu Matumoto, Junji Sasaki

(鈴木 達二) (松本 進) (佐々木 淳二)

and **Sannosuke Nunokawa.**

(布川 三之助)

(From the Physiological Laboratory of Prof. Y. Satake,
Tohoku University, Sendai.)

(Received for publication, March 27, 1951)

Having an intimate relation with acetylcholine, potassium ion is considered as an important factor in the synaptic transmission of nerve impulses. It was demonstrated that the potassium ion causes the liberation of acetylcholine when applied to the sympathetic cervical ganglion,¹⁾ submaxillary gland, tongue, sweat gland²⁾ and heart.³⁾

Feldberg and Vartiainen⁴⁾ observed that the action of KCl on the perfused cervical sympathetic ganglion was enhanced to some degree after perfusion with eserine. According to Feldberg and Guimaraes,²⁾ the secretory effect of KCl on the submaxillary gland increases definitely after injection of eserine.

KCl has an accelerating action upon the adrenaline secretion, which was demonstrated on non-anesthetized dogs in our laboratory by Arai *et al.*⁵⁾ To know whether the adrenaline secreting action of KCl is likewise enhanced by eserine or not, the present studies were undertaken. Some authors reported the papers dealing with similar question, but we had found non-agreement in their experimental results.

Katz and Katz⁶⁾ experimented on with dial anesthetized, eviscerated cats with restricted circulation, using the rise of blood pressure and a retraction of the denervated nictitating membrane as an indicator of an augmented adrenaline secretion. KCl was injected into the central end of the coeliac artery before and after intravenous injection of eserine. Their experimental results were not constant. In some cases the augmented adrenaline secretion caused by KCl was not enhanced after eserine. However in some experiments eserine enhanced the action of KCl definitely.

* Reported at the XX Annual Meeting of the Japanese Physiological Society at Taihoku, July 1941. (Nihon Seiri Z., 1941, 6, 141; Jap. J. Med. Sci., Biophysics, 1943, 8, 16.)*

In the same year, Kohler and Lévy⁷⁾ reported the accelerating action of KCl upon the adrenaline secretion seemed to be not enhanced with eserine.

On the other hand, Hermann *et al.*⁸⁾ noticed a remarkable increase of the adreno-secretory action of KCl after eserine injection. Using the method of the suprarenal-jugular anastomosis, KCl was injected intravenously into the donor dog with the acutely or chronically denervated suprarenals before or after eserine injection. The elevation of blood pressure of a recipient dog caused by KCl after eserine was definitely intensiver than that before eserine.

In our experiments the effect of eserine upon the adrenaline secretory action of KCl was studied quantitatively on non-anesthetized dogs.

Method.

In dogs the D₁₁-L₈ dorsal spinal roots were cut under morphine-ether-narcosis, and about 4-11 weeks later the experiments were carried out. The suprarenal vein blood was sampled by using the lumbar route method of Satake *et al.*⁹⁾ without anesthesia, and the adrenaline in the suprarenal vein blood was estimated by means of the rabbit intestine segment method. The blood pressure was registered by a mercury manometer from the femoral artery. A small cannula for injection was inserted in the saphena vein.

KCl was injected in a dose of 30-38 mg per kg of body weight as a 3-10% solution intravenously in about 15 seconds. Just after the start of KCl-injection the sampling of suprarenal vein blood was started. The same dose of KCl was injected again 0.5-1 hour after the first KCl injection and some minutes before the second KCl-injection eserine was injected. Eserine salicyl. (Merk) was as a 0.05% solution in a dose of 0.3 mg per kg in 60 seconds intravenously injected. As a control experiment, eserine was not used in Exp. 1. Only KCl in the same dose was injected intravenously twice with the interval of half an hour.

Results.

To show the outline of the experimental procedures, an example (Exp. 5) is given in full in Tab. I. with the protocol the blood pressure tracings are produced in Fig. 1.

Exp. 1 (Control experiment) A male dog, 18.5 kg (9. V. 1941)

In this dog, KCl was injected intravenously in a dose of 33 mg per kg in 15 seconds. The animal excited slightly. The blood pressure fell transitorily from 87 mm Hg to 74 mm Hg within 13 seconds after the start of injection.

but soon it returned to the initial height. Some seconds later, the blood pressure began to fall promptly and 6 seconds later its lowest height of 47 mm Hg was reached. The rate of heart beat decreased. Then the blood pressure rose and resumed its initial height within 43 seconds after the start of injection.

The adrenaline secretion rate, which was 0.02–0.03 γ per kg per minute from one gland before injection, increased after KCl injection to 0.35 γ per kg per minute in the first thirty-second-period. In the second thirty-second-period, the secretion rate was somewhat larger than the initial rate but in the third thirty-second-period it was almost the initial value.

About half an hour, 33 mg KCl per kg of body weight was again injected intravenously in 15 seconds. The dog excited slightly. The blood pressure fell temporarily (during about 4 seconds) within 12 seconds after the start of injection. Some seconds later, the blood pressure began to fall from 94 mm Hg, and 4 seconds later it reached 53 mm Hg. The slowing of the heart beat occurred. Then the blood pressure turned to rise and recovered its initial height 31 seconds after the start of injection.

The adrenaline secretion rate before the second KCl injection was 0.02 γ per kg per minute. On the injection, it increased to 0.38 γ per kg per minute in the first thirty-second-period. In the second thirty-second-period, it resumed almost the pre-injection rate.

In this control experiment we ascertained that KCl in the same dose evoked the acceleration of adrenaline secretion of almost the same intensity.

Exp. 2 A male dog, 11.0 kg (19. IX. 1940)

KCl was injected intravenously in a dose of 30 mg per kg in 17 seconds. Excitement was not observed, but the pupils dilated. Within 9 seconds after the start of injection, the blood pressure fell temporarily from 95 mm Hg to 72 mm Hg and soon it returned to the initial height. The adrenaline secretion rate, which was 0.03 γ per kg per minute before the KCl injection increased to 0.39 γ . But soon the adrenaline secretion rate resumed almost the pre-injection value.

About an hour after the first KCl injection, 0.3 mg per kg of eserine was injected intravenously in 60 seconds. The pupils dilated. After the end of injection, the blood pressure rose gradually. The adrenaline secretion rate was 0.03–0.04 γ per kg per minute, within 4 minutes after eserine injection. 6 minutes later, the animal salivated and urinated.

11 minutes after eserine, 30 mg KCl per kg was again injected intravenously in 18 seconds. The blood pressure did not fall, but rose gradually after the end of injection. The adrenaline secretion rate was measured as 1.1 γ per kg per minute in the first thirty-second-period. With the next specimen, the secretion rate was measured as a double of the initial value, but thereafter it resumed nearly the rate of pre-injection.

Exp. 3 A female dog, 13.3 kg (8. X. 1940)

KCl was injected intravenously in a dose of 33 mg per kg of body weight in 15 seconds. The dog did not excite. Within 17 seconds after the start of injection, the blood pressure rose from 87 mm Hg to 98 mm Hg, but soon it began to fall and 9 seconds later its lowest height (55 mm Hg) was reached. The slowing of the heart beat occurred. Then the blood pressure rose up to 77 mm Hg within 36 seconds after the start of injection. The initial rate of adrenaline secretion of this dog was 0.02–0.03 γ per kg per min. On the injection, the secretion rate increased to 0.22 γ per kg per minute during the first thirty-second-period. With the specimen, which was collected in the second thirty-second-period, the rate of adrenaline secretion was about double as much as that of initial value but in the third thirty-second-period it resumed almost the pre-injection value.

About half an hour later, eserine was injected intravenously in a dose of 0.3 mg per kg of body weight in 60 seconds. Soon after eserine pupils dilated and the respiratory movements became deep and rough. Shivering was observed. The blood pressure rose gradually. The rate of the heart beat rather decreased. 5 minutes after eserine injection, the adrenaline secretion rate was 0.03 γ per kg per min.

8 minutes after eserine injection, 33 mg per kg KCl was again injected intravenously in 16 seconds. The animal urinated and defecated. The blood pressure rose gradually from 118 mm Hg and reached 142 mm Hg within 23 seconds after the start of injection. The adrenaline secretion rate increased definitely after the injection. In the first thirty-second-period, it was 1.7 γ per kg per min., and in the next thirty-second-period the secretion rate was 0.17 γ per kg per minute. With the specimen taken in the third thirty-second-period, it was still over the pre-injection value.

Exp. 4 A male dog, 19.2 kg (26. XI. 1940)

In this dog, KCl was injected intravenously in a dose of 38 mg per kg in 17 seconds. Within 13 seconds after the start of injection the blood pressure rose from 88 mm Hg to 98 mm Hg, but soon it began to fall and reached 56 mm Hg within 25 seconds after the start of injection. The rate of heart beat decreased. Then the blood pressure turned to rise and elevated to 92 mm Hg. The basal secretion rate of adrenaline was 0.03 γ per kg per min. On the KCl injection, the adrenaline secretion rate was found to have increased in the first thirty-second-period to 0.26 γ per kg per min. In the second thirty-second-period it was still somewhat larger than the initial value.

About half an hour after the first KCl injection, 0.3 mg per kg of eserine was injected in 60 seconds. The pupils dilated. The blood pressure rose from 88 mm Hg gradually after the end of injection. 2 minutes later 175 mm Hg was reached. The secretion rate of adrenaline was 0.04 γ per kg per minute. Then 38 mg per kg of KCl was again injected intravenously in 17 seconds. The blood pressure began to fall from 180 mm Hg within 20 seconds after the start of injection and 5 seconds later it reached 124 mm Hg. The rate of heart beat decreased. Then the pressure began to rise and reached

176 mm Hg. The adrenaline secretion rate in the first thirty-second-period was 0.7γ per kg per min. In the second thirty-second-period the secretion rate resumed nearly its pre-injection value.

Exp. 5 A female dog, 15.4 kg (3. XII. 1940)

The basal adrenaline secretion rate in this dog was 0.02γ per kg per minute. KCl was injected intravenously in a dose of 35 mg per kg in 15

Fig. 1. Blood pressure tracings in Exp. 5. (Reduced to 3/5). Dog 15.4 kg ♀, non-anesthetized.

KCl was injected intravenously in a dose of 35 mg per kg of body weight.

- (I) KCl injection before eserine.
- (II) KCl injection after eserine.

Time in seconds.

TABLE I.

Exp. 5. 3. XII. 1940 Dog ♀ 15.4 kg

Time	Time after KCl injection (sec.)	No. of specimen	Blood flow per kg per min. (cc)	Adrenaline in 1 cc blood (γ)	Adrenaline output per kg per min. (γ)	Blood pressure (mm Hg)	Heart rate (per min.)	Respiration (per min.)	Body temperature (C°)
31. X. 1940 15.3 kg D ₁₁ -I ₃ dorsal spinal roots severed. 9:50 a. m.-11:40 a. m. The left lumbar route preparation. The left femoral artery and the right saphena vein prepared.									
1:36 p.m.									39.0
1:45		1	0.49	0.05	0.02	86	150	30	
		2	0.41	0.05	0.02				
1:48									38.5
1:50		3	0.35	0.05	0.02	82	135	24	
1:55									38.3
2:10		4	0.43	0.05	0.02	85	159	23	
2:11	Injected intravenously 9.2 cc of 0.05% KCl (35 mg per kg) in 15 seconds.								
	0-30	5	0.57	1.0	0.57	85-39-66	168-60-168		
	30-60	6	0.53	0.05	0.03	66-35	168	30	
	60-90	7	0.56	0.05	0.03	85	168	26	
2:22									38.8
2:32		8	0.41	0.05	0.02	71	162	30	
		9	0.39						
2:33	Injected intravenously 9.2 cc of 0.05% eserine (0.3 mg per kg) in 60 seconds.								
2:33						68	150	27	
2:36						98	132	30	
2:37		10	0.60	0.05	0.03	112	132	51	
	Injected intravenously 18 cc of 3% KCl (35 mg per kg) in 16 seconds.								
	0-30	11	0.95	2.0	1.9	126-74-94	168-96-110		
	30-60	12	0.79	0.2	0.16	94-128-121	110-171	11	
	60-90	13	0.60	0.05	0.03	125	153	11	
2:45						112	168	30	39.0
2:47		14	0.51	0.05	0.03	111	171	52	
		15	0.49						
2:55						104	177	48	39.1
3:04						88	153	42	
3:09		16	0.41	0.05	0.02	92	162	45	
		17	0.43						
3:11									39.2

Room temperature 17-18 °C.

seconds. During the injection the animal barked. The blood pressure began to fall from 85 mm Hg within 12 seconds after the start of injection and 11 seconds later its lowest level (39 mm Hg) was reached. The rate of the heart beat decreased markedly. Then the blood pressure rose and 13 seconds later it returned almost to the initial height. The rate of adrenaline secretion measured

with the specimen taken in the first thirty-second-period was 0.57γ per kg per minute. In the second thirty-second-period, the rate of secretion resumed the initial value.

About twenty minutes after the KCl injection, eserine was injected intravenously in a dose of 0.3 mg per kg in 60 seconds. After finishing the eserine injection, the pupils dilated and the respiration became rough and deep. The blood pressure rose from 68 mm Hg gradually. Two minutes later, the animal struggled. The adrenaline secretion rate was 0.03γ per kg per min.

35 mg per kg of KCl was again injected intravenously in 16 seconds. The animal shivered. The blood pressure fell promptly from 126 mm Hg to 74 mm Hg within 20 seconds after the start of injection and lasted for 8 seconds. Slowing of the heart beat occurred. Then the blood pressure rose and returned to initial height 33 seconds after the start of injection.

The adrenaline secretion rate accelerated markedly after injection. It was 1.9γ per kg per minute in the first thirty-second-period. In the second thirty-second-period, the rate of adrenaline secretion was 0.16γ per kg per min. In the third thirty-second-period the secretion rate of adrenaline resumed the pre-injection value.

From the description quoted above, it is known that the accelerating action of KCl upon the adrenaline secretion of the suprarenals is enhanced by eserine.

SUMMARY.

In dogs, the suprarenal vein blood was collected without narcotizing. Adrenaline in the blood specimen was determined by means of the rabbit intestine segment method.

At first, $30\text{--}38\text{ mg per kg}$ of KCl was injected intravenously in 15 seconds. After about half an hour, 0.3 mg per kg eserine was injected intravenously in 60 seconds, and 4–11 minutes later KCl in a same dose was again injected. The adrenaline secretion after the second KCl injection was compared with that of the first KCl injection.

Before injection, the rate of adrenaline secretion from one gland was $0.02\text{--}0.03\gamma$ per kg per min. At the first KCl injection, it increased to $0.22\text{--}0.57\gamma$ per kg per min. After eserine, and before the second KCl injection, the rate of adrenaline secretion was $0.03\text{--}0.04\gamma$ per kg per min. At the second KCl injection, it increased to $0.7\text{--}1.9\gamma$ per kg per min.

Thus it is clear that the accelerating action of KCl upon the adrenaline secretion is enhanced by eserine.

References.

- 1 Brown and Feldberg, J. Physiol., 1935, **84**, 12 P; 1936, **86**, 297 ff.
- 2 Feldberg and Guimaraes, *ibid.*, 1936, **86**, 306.
- 3 Beznak, *ibid.*, 1934, **82**, 147 f.

- 4 Feldberg and Vartiainen, *ibid.*, 1935, **83**, 124 ff.
 5. Arai, Outi and Wada, *Nihon Seiri Z.*, 1940, **5**, 133; *Jap. J. Med. Sci., Biophysics* 1941, **7**, 69.*
 - 6 Katz and Katz, *Proc. Soc. Exp. Biol. & Med.*, 1937, **36**, 848.
 - 7 Kohler and Levy, *C. R. Soc. Biol.*, 1937, **126**, 405.
 - 8 Hermann, Jourdan, Morin and Vial, *ibid.*, 1938, **127**, 613; 1938, **128**, 676.
 - 9 Satake, Sugawara and Watanabe, *Tohoku J. Exp. Med.*, 1927, **8**, 501.
-