EFFECT OF NICOTINE ON SERUM POTASSIUM AND BLOOD GLUCOSE

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It has been shown by D'silva (1) and others (2-4) that the intravenous injection of adrenaline into the cat, rabbit, or dog causes a transient and marked increase in serum potassium level. The liver has been established as the major source of the extra potassium in adrenaline hyperkalemia (5-7).

On the other hand, nicotine stimulates adrenaline release from the adrenal glands (11-13), thereby the hyperglycemia is produced as the result of a pharmacological action of nicotine (14-16). As the authors are interested in the relation of the hepatic release of potassium to the glycogenolysis, the effect of nicotine on serum potassium level was observed, in the above-cited situation, and compared with its hyperglycemic potency.

METHODS

Dogs, weighing 7 to 10 kg, were fasted for 18 to 20 hours and anesthetized with intraperitoneal injection of pentobarbital sodium (35 to 45 mg/kg). Arterial blood samples were collected in glass centrifuge tubes through polyethylene tube inserted into femoral artery. The first few drops of each sample were discarded in order to ensure that sample of 2.0 to 3.0 ml to be from real circulating blood. Blood samples were centrifuged for 10 minutes at 3,000 r.p.m.. Serum potassium was determined with a Beckman-type flamephotometer and blood glucose was determined by the method of Somogyi-Nelson (17).

In some experiments, adrenalectomized dogs were used and fed on regular food and tap water containing NaCl *ad libitum*. They were also given intramuscularly 50 mg of cortison, penicilline (4×10^{-7} units) and 500 mg of streptomycine daily.

RESULTS

1. Serum potassium and blood sugar levels following the administration of nicotine in anesthetized dogs

The mean values of normal serum potassium and blood glucose concentration are 4.2 mEq/l $\pm$ 0.05 and 82 mg/dl $\pm$ 1.3, respectively (Table 1).

Changes of serum potassium and blood glucose after nicotine injection are shown in Table 2. A typical case is shown in Fig. 1.

TABLE 1. Normal serum potassium and blood glucose values in anesthetized dogs.

	Serum potassium (mEq/l)	Blood glucose (mg/dl)
Mean	4.2	82
S.E.	± 0.05	± 1.3
N	60	60

N : The number of animals

TABLE 2. Serum potassium and blood glucose changes following administration of nicotine (100 μ g/kg, i.v.) in anesthetized dogs.

Exper. No.	Serum potassium (mEq/l)		Blood glucose (mg/dl)	
	Control level	Maximum increase over control	Control level	Maximum increase over control
1	4.4	1.8	83	56
2			81	43
3	4.2	2.5		
4	4.2	2.5	77	34
5	3.8	3.4		
6	4.8	3.7		
7	4.0	3.4	68	42
8	4.2	2.5		
9	4.4	3.1	68	54
10	4.4	2.4	90	34
11	4.1	1.6	72	38
12	3.4	4.0		
Mean	4.2	2.8	77	43
S.E.	± 0.1	± 0.3	± 3	± 3

FIG. 1. Time course of hyperkalemic and hyperglycemic responses to nicotine in anesthetized dogs.

Nicotine (100 μ g/kg) was intravenously injected at time $\uparrow$.

The intravenous injection of 100 $\mu\text{g/kg}$ of nicotine caused a transient increase in serum potassium level, which reached its maximum in 60 to 90 seconds and returned to the control level in 4 to 5 minutes. In most experiments the potassium level fell below the control level before the final return to resting level. The average value of maximum rises in serum potassium was 2.8 mEq/l above the control level (Table 2).

FIG. 2. Inhibitory effect of C_6 on hyperkalemic and hyperglycemic responses to nicotine.

C_6 was intravenously injected 8 minutes before administration of 100 $\mu\text{g/kg}$ of nicotine in anesthetized dogs.

Nicotine-induced hyperglycemia reached its peak much later than the hyperkalemia did and the period of hyperglycemia persisted much longer than the hyperkalemia. The average value of maximum rises in blood glucose was 43 mg/dl above the control level (Table 2).

The increases in serum potassium and blood glucose levels were proportional to the dose of nicotine administered (Fig. 2).

2. Effect of hexamethonium on nicotine-induced hyperkalemia and hyperglycemia

As shown in Fig. 3, pretreatment with 1 to 3 mg/kg of hexamethonium bromide inhibited the hyperkalemic and hyperglycemic responses to 100 $\mu\text{g/kg}$ of nicotine.

FIG. 3. Comparison of the changes in serum potassium and blood glucose concentrations of normal and of adrenalectomized dogs following administration of nicotine.

Nicotine (100 $\mu\text{g/kg}$) was intravenously injected at time $\uparrow$.

3. Hyperkalemic and hyperglycemic responses to nicotine in adrenalectomized dogs

The serum potassium concentrations in adrenalectomized dogs were slightly higher than those in normal dogs and the mean value was $4.9 \text{ mEq/l} \pm 0.4$.

The effect of nicotine on the serum potassium and blood glucose concentration in adrenalectomized dogs is shown in Fig. 4. In adrenalectomized dogs hyperkalemic response to nicotine was markedly lower than in normal dogs. The maximum increases in plasma potassium following $100 \mu\text{g/kg}$ of nicotine ranged 0.5 to 0.8 mEq/l above the control level. Hyperglycemia was not observed after $100 \mu\text{g/kg}$ of nicotine in adrenalectomized dogs and in some cases a slight decrease in blood glucose concentration was observed following the administration of nicotine.

4. Effect of atropine on the hyperkalemic response to nicotine

Hyperkalemia and hyperglycemia was not observed within 8 minutes after 12 mg/kg of atropine alone.

Table 3 shows the hyperkalemic and hyperglycemic responses to nicotine in dogs pretreated with 2 mg/kg of atropine. The average value of maximum rise in plasma potassium after $100 \mu\text{g/kg}$ of nicotine in atropine-treated dogs was 1.8 mEq/l , without reducing the hyperglycemic response to nicotine.

FIG. 4. Effect of atropine on hyperkalemic response to nicotine in adrenalectomized dogs.

Atropine (2 mg/kg) was intravenously injected 8 minutes before intravenous injection of nicotine ($100 \mu\text{g/kg}$).

○—○ : Atropine dogs
●---● : Untreated dogs

TABLE 3. Effect of atropine on hyperkalemic and hyperglycemic responses to nicotine in anesthetized dogs.

	Maximum increase over control		Maximum increase over control	
	Serum potassium (mEq/l)		Blood glucose (mg/dl)	
	Atropine		Atropine	
	—	+	—	+
Mean	2.8	1.8	43	47
S.E.	± 0.3	± 0.3	± 3	± 3
N	11	5	7	3

Atropine (2 mg/kg) was intravenously injected 8 minutes before intravenous injection of nicotine ($100 \mu\text{g/kg}$).

N: The number of animals.

FIG. 5. Comparison of effects of adrenaline and nicotine on serum potassium and on blood glucose levels.

Drugs were intravenously injected at time $\uparrow$.

○—○ : Adrenaline 2.5 $\mu\text{g/kg}$, i.v.

●---● : Nicotine 100 $\mu\text{g/kg}$, i.v.

TABLE 4. Serum potassium and blood glucose changes following administration of adrenaline (2.5 $\mu\text{g/kg}$, i.v.) in anesthetized dogs.

	Serum potassium (mEq/l) Maximum increase over control	Blood glucose (mg/dl) Maximum increase over control
Mean	1.9	45
S.E.	± 0.2	± 3
N	10	8

N : The number of animals

Table 4.

The maximum increase in serum potassium concentration induced by nicotine (100 $\mu\text{g/kg}$) was a little greater than that induced by adrenaline (2.5 $\mu\text{g/kg}$) but nicotine was almost equivalent to adrenaline in hyperglycemic potency at the same dose level. The peak of hyperkalemia and hyperglycemia induced by adrenaline was attained a little earlier than those induced by nicotine.

DISCUSSION

It was discovered that nicotine produced a transient rise in arterial serum potassium concentration. The hyperkalemia induced by nicotine passed in a few minutes while

5. Comparison of nicotine and adrenaline in hyperkalemic action

Results above-mentioned indicate that nicotine-induced hyperkalemia was mainly mediated through a release of adrenaline from the adrenal glands, and therefore, hyperkalemic effect of nicotine was compared with that of adrenaline. A typical case is shown in Fig. 5 and the effect of adrenaline on the serum potassium concentration and blood glucose is shown in

the hyperglycemia persisted for longer.

It has been known that nicotine can induce a temporary increase in the secretion of adrenaline from the adrenal medulla (11-13). On the other hand, adrenaline is also known to cause the hyperkalemia in animal of various species (1-4). It is possible that the rise of serum potassium after nicotine administration is mediated through the release of adrenaline. The removal of adrenal glands markedly reduced the hyperkalemic responses to nicotine. It was also demonstrated that hexamethonium inhibited the nicotine-induced hyperkalemia. De Schaepdryver (18) and Woods *et al.* (19) reported that hexamethonium inhibited the stimulating action of nicotine on adrenal secretion. These data seem to indicate that the liberation of potassium by nicotine is mainly mediated through a release of adrenaline from adrenal glands. A little rise in serum potassium concentration was, however, still observed in adrenalectomized dogs.

Parrot *et al.* (20) reported that histamine released potassium from isolated guinea pig ileum. It was also shown that injection of histamine caused the rise of plasma potassium level (21-23). Macmillan *et al.* (23) suggested that increased potassium in plasma after histamine was not mediated through a release of adrenaline from adrenal glands, but it was a result of the contraction of smooth muscle induced by histamine. So it is possible that stimulating action of nicotine on autonomic ganglion and neuromuscular junction causes liberation of potassium. Then a further study was made employing atropinized dogs. The treatment with atropine reduced the hyperkalemic response to nicotine in normal dogs and abolished the hyperkalemic response to nicotine in adrenalectomized dogs. These results suggest that smooth muscle stimulated by nicotine may be a minor source of the increase in serum potassium concentration following the administration of nicotine.

It has been reported that several drugs other than adrenaline reveal the hyperkalemia. These drugs may be separated into two groups in terms of mechanism of action. These are: 1) adrenaline (1-7), sympathomimetic amines (24, 25), glucagon (26), ether (27) and posterior pituitary extract (27), 2) histamine (21-23), BaCl_2 (23) and acetylcholine (23). Drugs belong to the first group seem to act directly on the liver and/or through catecholamine release from the adrenal glands followed by potassium release from the liver. Second group of drugs seem to release potassium from smooth muscle by their stimulating action. Although nicotine acts through both mechanisms forementioned, the principal mechanism of hyperkalemia induced by nicotine is its stimulating action on adrenal glands.

Then, the hyperkalemic and hyperglycemic responses to nicotine were compared with those to adrenaline and hyperkalemic effect of 100 $\mu\text{g/kg}$ of nicotine was found greater than that of 25 $\mu\text{g/kg}$ of adrenaline. Reduction of hyperkalemic response to nicotine by pretreatment with 2 mg/kg of atropine is equivalent to the difference of responses between to nicotine and to adrenaline. One hundred microgram per kilogram of nicotine was almost equivalent in hyperglycemia to 2.5 $\mu\text{g/kg}$ of adrenaline. Nicotine-induced hyperglycemia is caused by catecholamine released from adrenal glands. There-

fore, it seems likely that intravenous injection of 100 $\mu\text{g/kg}$ of nicotine causes libelation of catecholamine corresponding to 2.5 $\mu\text{g/kg}$ of exogeneous adrenaline.

SUMMARY

It was demonstrated that intravenous administration of nicotine caused a transient increase in plasma potassium level which had a peak at 60 to 90 seconds and returned to the control level in 5 to 8 minutes in nembutal anesthetized dogs. The changes in serum potassium and blood glucose were proportional to the dose of nicotine. The hyperkalemia and hyperglycemia induced by 100 $\mu\text{g/kg}$ of nicotine were almost completely inhibited by 3 mg/kg of hexamethonium. The pretreatment with atropine (2 mg/kg) slightly inhibited the hyperkalemic response but not the hyperglycemic response to nicotine. In adrenalectomized dogs, the nicotine hyperkalemia was markedly less than in the normal, and disappeared with 2 mg/kg of atropine. The hyperkalemic response to 100 $\mu\text{g/kg}$ of nicotine was a little greater than that of 2.5 $\mu\text{g/kg}$ of adrenaline. Atropine abolished this difference of responses between to nicotine and to adrenaline. These results indicate that nicotine hyperkalemia is mainly mediated through a release of adrenaline from the adrenal gland and partially through the contraction of smooth muscle.

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