

EFFECT OF CENTRALLY ADMINISTERED GLUCAGON ON URINARY SODIUM AND POTASSIUM CONCENTRATION IN DOGS

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Summary: The effects of glucagon administration through intracerebroventricular (ICV), third ventricular (TV) and intracisternal (IC) routes on urinary sodium and potassium concentration have been studied in mongrel dogs. The central administration of glucagon resulted in a significant decrease in urinary sodium concentration ($P < 0.01$) and increase in urinary potassium concentration ($P < 0.001$). This change in urinary sodium and potassium concentration on central administration of glucagon was abolished in animals which were vented to either sympathetic denervation or adrenalectomy.

The observations in the present study suggest that the changes in urinary sodium and potassium concentration on central administration of glucagon, are due to increased secretion of some substance from the adrenals and the probable efferents might be the sympathetic fibres.

Key words: glucagon central sodium potassium

INTRODUCTION

Previously we showed that central administration of glucagon produced a significant oliguric effect which was abolished in sympathetic denervated or adrenalectomised dogs (1). This led us to assume that glucagon does not pass the brain-blood barrier, and the effects observed when glucagon was administered into lateral ventricle of the brain were due to its direct action on the central nervous system (CNS).

The aim of the present investigation was to extend those observations and to find out the role of aldosterone in terms of urinary sodium and potassium excretion in animals.

MATERIALS AND METHODS

The study was conducted in 50 adult mongrel dogs of either sex, weighing between 10 to 12 kg. The animals were fasted 10 hrs before being anaesthetised by a slow injection of chloralose (80 mg/kg body weight) in a leg vein.

In 33 animals the intracerebroventricular cannula was anchored in left lateral ventricle of the brain by the technique of Feldberg *et al.* (6). A successful insertion of the cannula into the brain ventricle and the evidence for any lesions in the surrounding tissues were checked by the technique of Agarwala *et al.* (2). In ten of the early experiments it was confirmed that the glucagon solution administered through the ICV-cannula actually reached the ventricle because carbon-black (added to glucagon solution) was found in all the ventricles of the brain during autopsy (12).

The third-ventricular (TV) administration of glucagon was done in 6 animals by the technique of Zucker *et al.* (17) and in 6 animals the intracisternal administration was done by the technique of Chowars *et al.* (4).

The experiments (ICV) were repeated on animals after the following acute surgical procedures:

- (i) Spinal-cord transectomy along with vagosympathectomy (SCT-VST) was done in 11 animals by the technique of Agarwala *et al.* (1).
- (ii) Adrenalectomy was done in 11 animals by the technique of Edwards (5).

In a separate set of experiment, the effect of intravenous (I/V) administration of glucagon on urinary sodium and potassium concentration was observed in 5 normal animals.

In all the experiments, normal saline was infused in animals at the rate of 1.0 ml/min. A period of 1 hr was allowed to elapse between the surgical preparation and the dose administration. The right femoral artery was connected to a mercury manometer so as to record mean blood pressure of the animal. After the planned surgical procedure, both ureters were visualized per abdomen and were cannulated with polyethylene catheters. The urine samples were collected in polyethylene tubes at 15 min interval for a period of 2 hrs after the dose administration. The volume of urine was measured at once and the urinary sodium and potassium concentration was estimated by the flame photometer in a sample taken from the total volume of urine collected in 2 hrs.

Glucagon solution and its dose:

Glucagon solution was prepared (1) and a dose of 2.0 μg in 0.2 ml solution was administered in all the experiments. The solution of glucagon injected into lateral ventricle of the brain so as to confirm that the solution injected through the ICV-cannula actually reached the ventricle, was prepared by mixing 4 parts of glucagon (2.0 μg) in normal saline with 1 part of a suspension of carbon-black in normal saline.

The control experiments were carried out by administering inactivated glucagon solution (2.0 μg in 0.2 ml) via ICV-route in normal, SCT-VST and adrenalectomised animals. The inactivation of glucagon was done by alkalization and heating in a boiling water-bath for 20 min. The pH of the solution was adjusted to that of the glucagon solution (Table I).

The results expressed are the means \pm SE after applying the Student 't' test.

RESULTS

The intravenous administration of glucagon in normal animals caused an insignificant ($P > 0.05$) rise in urinary sodium concentration without a change in urinary potassium concentration and mean blood pressure. Conversely, the glucagon administration via ICV-route resulted in a significant ($P < 0.01$) fall in urinary sodium concentration for 54.4 ± 5.1 mEq/L

TABLE I: Mean values of urine volume (U. Vol.), urinary sodium (UNa) and potassium (UK) concentration and mean blood pressure (B.P.) after ICV administration of inactive glucagon solution in normal, spinal-cord transectomised-vagosympathectomised (SCT-VST) and adrenalectomised (Adx) control animals. (n=5 in each group)

Animal		Initial value at 0 hr	Maximum value
Normal	U. Vol.	3.2±0.2	3.0±0.3 ml/15 min
	U _{Na}	128.0±6.4	122.6±8.3 mEq/L
	U _K	108.6±7.2	110.1±6.2 mEq/L
	B.P.	106.8±4.5	109.6±5.4 mm of Hg
SCT-VST	U. Vol.	2.8±0.4	2.6±0.4 ml/15 min
	U _{Na}	120.1±8.3	126.4±6.2 mEq/L
	U _K	110.0±6.6	106.2±4.8 mEq/L
	B.P.	108.0±5.8	100.6±6.0 mm of Hg
Adx	U. Vol.	2.5±0.3	2.4±0.3 ml/15 min
	U _{Na}	118.6±8.8	114.3±7.3 mEq/L
	U _K	110.5±6.3	110.2±6.8 mEq/L
	B.P.	96.2±8.8	92.6±6.7 mm of Hg

and rise in urinary potassium concentration for 37.6±4.6 mEq/L (P<0.001) whereas, there was no appreciable change in mean blood pressure (Table II).

In order to study the role of efferents in transmission of impulses from CNS to various organs, glucagon administration was done in spinal-cord transectomised-vagosympathectomised (sympathetic denervated) animals; there was no change in either of the observations (Table II).

In an attempt to find out the organ involved in producing a change in urinary sodium and potassium concentration after the central administration of glucagon: when the animals were adrenalectomised, no change was observed (Table II). Moreover, to precisely localize the site of action of centrally administered glucagon, three possible routes (ICV, TV, IC) were considered. The observations obtained when glucagon was administered via IC route, in comparison to ICV and TV routes, were found to be most significant (P<0.001): there was a marked fall in urinary sodium concentration for 67.5 5.1 mEq/L and rise in urinary potassium concentration for 43.9±4.5 mEq/L without a change in mean blood pressure of the animal (Table II).

TABLE II: Mean values of urine volume (U. Vol.), urinary sodium (U_{Na}) and potassium (U_K) concentration and mean blood pressure (B.P.) after glucagon administration via intravenous (I/V) and central routes in animals.

Route	Surgical procedure	No. of animal		Initial value at 0 hr	
				U. Vol. ml/15 min, B.P. mm of Hg.	U _{Na} & U _K mEq/L
I/V	Normal animal	5	U. Vol.	3.1±0.3	3.9±0.2 ^{''}
			U _{Na}	136.2±8.0	148.1±4.6 [']
			U _K	112.0±6.2	110.6±8.1
			B.P.	108.0±10.0	107.2±6.0
ICV	Normal animal	6	U. Vol.	3.6±0.2	1.1±0.3**
			U _{Na}	122.6±8.2	68.2±5.1*
			U _K	108.0±3.8	145.6±4.6**
			B.P.	110.0±8.0	106.2±5.2
	Spinal-cord transectomised -vagosympathectomised animal	6	U. Vol.	2.6±0.3	2.2±0.4 [']
			U _{Na}	118.6±6.2	111.0±5.3 [']
			U _K	114.2±7.9	110.5±6.6
			B.P.	90.6±8.8	86.8±7.6
	Adrenalectomised animal	6	U. Vol.	2.1±0.4	2.0±0.4 [']
			U _{Na}	102.0±12.4	100.8±14.3
			U _K	96.8±10.0	98.2±12.6
			B.P.	82.3±7.9	80.0±10.0
TV	Normal animal	6	U. Vol.	3.2±0.2	1.3±0.4**
			U _{Na}	132.8±6.1	84.3±5.8*
			U _K	106.2±6.0	148.6±4.6*
			B.P.	118.2±6.7	110.2±10.0
IC	Normal animal	6	U. Vol.	3.1±0.4	0.5±0.2**
			U _{Na}	128.1±6.8	60.6±5.1**
			U _K	112.2±4.6	156.1±4.5**
			B.P.	114.2±8.0	112.0±6.2

[']P>0.05^{''}P<0.05

*P<0.01

**P<0.001

The administration of inactive glucagon via ICV route in different group of animals did not cause a change in urinary sodium and potassium concentration.

DISCUSSION

The observations of the present study support our previous results that centrally administered glucagon produced an oliguric effect in dogs and this effect which was observed irrespective to hyperglycaemia (2) was suggested to be due to stimulation of aldosterone secretion from the adrenals via the sympathetic fibres (1).

The fact that glucagon does not pass the brain-blood barrier (1) is further substantiated in the present investigation as no change in urinary sodium and potassium concentration on central administration of glucagon, is observed in spinal-cord transectomised-vagosympathectomised (sympathetic denervated) animals. Moreover, it further excludes the 'possible role of renal blood flow (9,15) to cause oliguria in animals where glucagon was administered centrally inasmuch as no change in mean blood pressure is observed during the course of an experiment.

Aldosterone has long been known to be secreted from the adrenals, is a potent antidiuretic agent (7, 8, 14) which causes retention of sodium and water whereas, it increases urinary potassium excretion (7, 9, 10,13). Similarly, in the present study, a significant decrease in sodium and water as well an increase in potassium excretion in urine is observed after the central administration of glucagon in normal animals. This role of aldosterone is further supported by our observations that adrenalectomy in animals abolished the effects of centrally administered glucagon on urinary sodium and potassium concentration.

The attempt to precisely localise the site of action of centrally administered glucagon has not yielded conclusive result but the observations from IC administration as compared to those obtained by ICV and TV routes does support the sites proposed by Jungmann *et al.* (11) and Wise *et al.* (16) viz the glucagon-sensitive receptors are located in or near the vicinity of the fourth ventricle of brain.

Although much more work is required to determine fully the role of centrally administered glucagon in the regulation of renal function, the results presented here support our previous view (1) that the centrally administered glucagon plays a role in the electrolyte and water balance.

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