Natriuresis Induced by Injection of Hypertonic Saline into the Third Cerebral Ventricle of Dogs* (33849)

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(Introduced by David Lehr)

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A considerable amount of evidence implicates the central nervous system in the regulation of sodium excretion and serum sodium levels. Sustained hypernatremia follows superficial cauterization of brain tissue in and around the cat hypothalamic supraoptic nucleus (1). Large urinary sodium losses result in rats after small bilateral posterior hypothalamic lesions (2), and threefold increases in sodium excretion persist 24 hr after destruction of the rat paraventricular hypothalamic nucleus (3). Increased sodium excretion not related to changes in the filtered load of sodium has been observed upon electrical stimulation of the pons in dogs (4). Hypertonic saline injected into the third ventricle of conscious goats has been reported to induce a natriuresis (5). The present report describes the effects on sodium excretion of injections of both isotonic and hypertonic NaCl into the third cerebral ventricle of anesthetized dogs. In several animals we have performed simultaneous measurements of blood pressure, glomerular filtration rate (GFR), and effective renal plasma flow (ERPF).

Methods. Female mongrel dogs weighing between 15–20 kg were anesthetized with pentobarbital (30 mg/kg iv). The third cerebral ventricle was cannulated by a procedure similar to that described by Soria (6). A 21-gauge hypodermic needle was used as the cannula. Urine was collected through a Foley retention catheter. Following three 0.5 hr control periods a single 0.4-ml injection of either isotonic NaCl or 5% NaCl was administered through a 1-ml syringe attached to the needle hub. Half-hr urine collections were continued for 3.5 hr after injection. In three of the dogs injected with 5% NaCl, GFR and ERPF were measured using inulin and para-aminohippurate clearances, respectively. Arterial blood pressure was measured through a femoral artery with a Statham strain gauge. Plasma and urine samples were analyzed for sodium by flame photometry using an internal lithium standard.

At the conclusion of each experiment the brain, with cannula intact, was removed from the skull and examined grossly for needle localization. In a few instances when it was not possible to delineate the implant site by gross observation, frozen sections of appropriate brain areas were cut at 40 μ and stained with cresyl violet to show cellular damage. In two dogs injected with 5% NaCl the cannula was not in the third ventricle. These animals are included in Figs. 1 and 2 as a separate group.

Results In Fig. 1 are plotted the mean changes in sodium excretion rate for each 0.5 hr collection period. In the group injected with hypertonic NaCl into the third brain ventricle (8 dogs) sodium excretion increased above control values in the first 30 min and remained elevated for the duration of the experiment. In contrast to the above, the group that was injected with isotonic NaCl (6 dogs) exhibited a reduction in sodium excretion which never rose above control values. The differences in changes in sodium excretion between the two groups are significant (Student's t test) at the 0.05 level for the 30-, 60-, 90-, and 120-min periods, at the 0.1 level for the 150- and 180-min periods, and at the 0.2 level for the 210-min period. In these last three periods the variability in sodium excretion was great, due, perhaps, to some decline in the depth of anesthesia.

In Fig. 2 are graphed changes in urine flow

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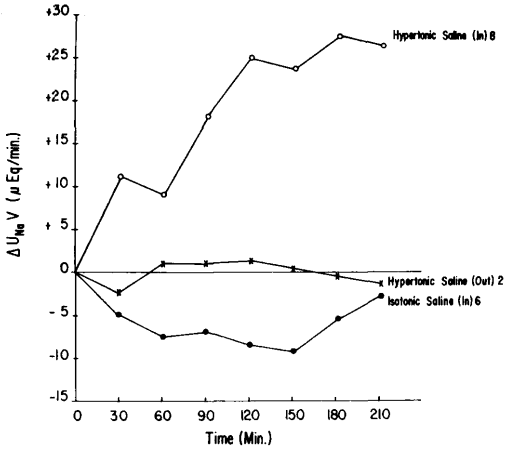

FIG. 1. Time course of the mean change in sodium excretion rate: each point represents the average change in sodium excretion of individual dogs from their own control (preinjection) levels. The group labelled hypertonic saline (out) represents the two dogs in whom the cannula was not in the third ventricle.

rate for the same three groups of dogs. In the hypertonic group urine flow increased immediately after injection and remained elevated throughout the experiment. In dogs that received isotonic NaCl urine flow first decreased below control levels and then rose so that at 180 and 210 min it was above control values. The difference in changes in urine flow between the two groups is significant at the 0.05 level for the 30-, 60-, and 90-min periods, and at the 0.1 level for the 120-, 150-, and 180-min periods. In the two dogs in which the cannula was not in the third ventricle both sodium excretion and urine flow did not appear to increase.

In the three dogs in whom renal functions were measured the percentage of the filtered load of sodium excreted rose after the injection of hypertonic saline and continued to do so for the duration of the experiment, while GFR and filtered load of sodium did not rise. Renal plasma flow remained constant. Blood pressure in these three animals fell slightly (5–10 mm Hg) immediately after injection, rose within 3 min to levels greater than control (Δ 10–20 mm Hg) and then slowly returned to control levels over a period of 1–2 hr.

Discussion. After injection of 5% NaCl into the third brain ventricle sodium concentration in the urine rose in much greater proportion than did the urine flow rate. At the end of 120 min the urine sodium concentration was on the average three times the control level, while urine flow had only increased by one-third. This might possibly be explained if the intraventricular injection of hypertonic saline enhanced sodium excretion and also stimulated ADH release. ADH would tend to decrease urine flow while the inhibition of sodium reabsorption should result in a diuresis.

The stimulus for sodium excretion in the absence of alterations in ERPF and GFR is probably not mediated via the renal nerves. Stimulation of the renal nerves results in decreased ERPF and intense stimulation in decreased GFR as well (7). In dogs denervated kidneys respond to electrical stimulation of certain regions of the pons with a natriuresis (4) and renal denervation fails to abol-

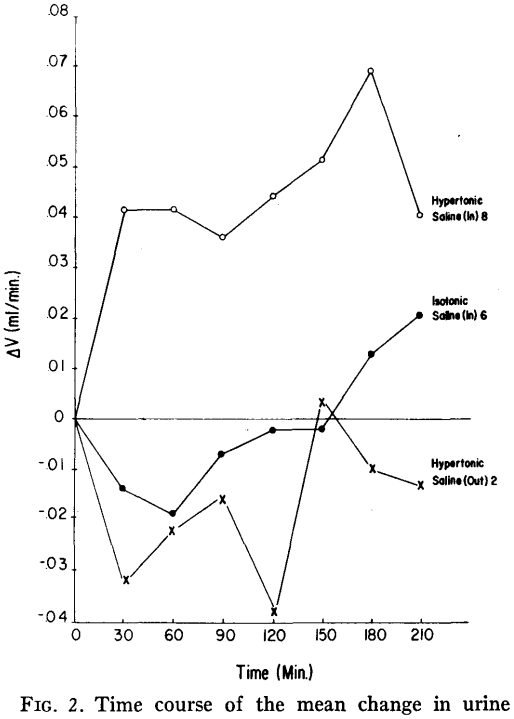

FIG. 2. Time course of the mean change in urine flow rate: each point represents the average change in urine flow rate of individual dogs from their own control (preinjection) values.

ish the natriuretic response to volume loading (8). Although it is possible that in our experiments part of the natriuresis may have been related to an inhibition of aldosterone secretion, it should be noted that Andersson *et al.* (5) obtained a natriuresis after hypertonic saline injection of the third cerebral ventricle of conscious goats who were given exogenous aldosterone throughout the experiment. In light of the above considerations, and in the absence of any evidence for a direct effect of the renal nerves on tubular sodium excretion, it appears quite likely that the natriuretic response is hormonally mediated.

Much evidence has accumulated in the past few years for the existence of a natriuretic hormone which after isotonic or hypertonic, systemic saline loading inhibits proximal tubular sodium reabsorption (9–11). Cross-perfusion experiments have not given conclusive confirmation for the presence of such a hormone (12, 13), although plasma from saline-loaded rats has been reported to inhibit proximal tubular sodium reabsorption in normal rats (14). That this postulated hormone originates in the central nervous system is supported by the experiments of Cort (15) who found a natriuretic peptide in jugular venous blood of cats undergoing a natriuresis following bilateral carotid artery occulusion, by those of Lockett (16) who reported that plasma from saline-loaded donor cats causes a natriuresis in an isolated perfused kidney and that this effect is eliminated by decapitation of the donor animal and by those of Rector *et al.* (17) who observed that the high natriuretic activity found in jugular venous plasma of saline-loaded rats is abolished by ablation of the median eminence.

The identicalness of a natriuretic factor whose secretion is stimulated by systemic volume loading and one whose release follows injection of the third ventricle with hypertonic NaCl is conjectural. It is conceivable that two hormones exist, one responsive to alterations in volume, the other to changes in the concentration of sodium. These hormones acting in concert could serve as an hormonal modulator of total body sodium. In any event, the natriuresis following injection of hypertonic NaCl into the third cerebral ventricle of anesthetized dogs appears to implicate this area of the brain as part of an, as yet, unidentified control mechanism regulating urinary sodium excretion.

Summary. Injection of 5% sodium chloride into the third cerebral ventricle of anesthetized dogs induced a significant increase in urinary sodium excretion not related to alterations in renal plasma flow, glomerular filtration rate, or the filtered load of sodium. The above findings are consistent with the action of a cerebral natriuretic hormone.

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