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# BRIEF COMMUNICATION

# Pitressin-Induced Inhibition of Drinking Following Water Deprivation in the SWR/J Mouse

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SCHMALBACH, N. L. AND C. L. KUTSCHER. *Pitressin-induced inhibition of drinking following water deprivation in the SWR/J mouse.* PHARMAC. BIOCHEM. BEHAV. 4(2) 203–205, 1976. – SWR/J female mice, 8 hr water deprived, were injected intraperitoneally with 0, 10, 50, 200, and 800 mU of aqueous pitressin, 5 min prior to presentation of water. Drinking measurements made at 5, 15, 25, and 35 min of the drinking period revealed a significant transient inhibition of drinking for the three highest dosages. Injections had no measureable effect on blood pressure. Only the highest dosage had an effect on gross motor activity, a significant decline.

Activity ADH Blood pressure Drinking Pitressin

ANIMALS respond to a water deficit by drinking to replace the lost water and by decreasing the rate of renal water excretion by means of the release of the antidiuretic hormone (ADH). There is reason to believe that these two processes may be functionally related.

First, the same internal stimuli may trigger and modulate both processes. Increases of less than 2% in the osmolality of plasma resulting in cellular dehydration, presumably detected by the hypothalamic osmoreceptors [20], and depletion of the extracellular fluid volume [18] are known to precipitate ADH release. These same stimuli are believed to precipitate drinking [9, 10, 11].

Secondly, it is possible that ADH release may have a direct effect on the initiation and volume of water intake. There is evidence in dogs indicating that ADH can facilitate drinking. Injection of Pitressin (an aqueous solution of the pressor principle of the posterior pituitary gland, substantially free of the oxytocic principle) into water-deprived dogs increased subsequent water intake [2]. In another experiment, dogs were infused intravenously with a hypertonic NaCl solution until threshold for drinking was reached. Dilute Pitressin injections reduced this threshold [19]. If ADH initiates or facilitates drinking, it is possible that its release may help to explain at least part of the dipsogenic effects of angiotensin [8] since there is evidence that stimulation of the renin-angiotensin system can cause ADH release [5].

However, Pitressin injections have also been found to inhibit drinking or to have no effect on drinking, apparently dependent upon the species used, state of water balance of the animal and the details of the experimental procedure [17]. Human patients with diabetes insipidus, severely dehydrated by 8 hr of water deprivation, have reported that a single injection of Pitressin temporarily depressed and then eliminated the urge to drink [15]. Pitressin in large doses inhibited drinking to NaCl injection in dogs [13,19]. In rats Pitressin has been found to have no effect or an inhibitory effect on drinking when testing was done under a variety of water balance conditions [1, 8, 16, 17], but the inhibitory effect may be weak or unreliable [17].

The effect of Pitressin on drinking was studied here in the SWR/J mouse strain because this strain develops an age-dependent nephrogenic diabetes insipidus [13] in which the kidneys become refractory to Pitressin [14], thus facilitating the experimental separation of renal from extrarenal Pitressin effects.

## METHOD

### *Animals*

Fifteen naive, female SWR/J mice, age 19–21 months were used in the experiment. At this age kidneys are known to be refractory to ADH [14]. Mean body weight at the beginning of the experiment was 25.7 g.

### *Apparatus*

Mice were housed individually in steel cages 12.5 × 12.5 × 14.5 cm, with tops of 0.6 cm mesh hardware cloth and solid bottoms covered with Sterolit (clay) bedding. Water was given in 100 ml gas measuring tubes with stainless steel

drinking spouts. Lights were on for 12 hr/day. Temperature was maintained at 21 ± 1° C. Air was humidified during the winter months.

Activity was measured in a Lehigh Valley Activity device. Movement of the animal interrupted two banks of photobeams and advanced a counter.

Systolic blood pressure was measured indirectly with a Narco Bio-Systems apparatus consisting of a Model DMP-4B physiograph and a Model PE-300 programmed electrosphygmomanometer.

*Procedure*

Tests were conducted in the order in which they are described.

*Drinking.* Mice were injected intraperitoneally with 0.1 ml of the aqueous form of Pitressin (Parke-Davis, Detroit, Michigan) in the following dosages given in an order randomized for each animal: 0 mU (demineralized water serving as control injection), and 10, 50, 200, and 800 mU. Tests were conducted on alternate days. On the test day, at the end of 8 hr of water deprivation, food was removed from the cage and injections were made. Five min were allowed for absorption of the injection before drinking tubes were placed on the cage for the 35 min drinking period. Water intakes were measured at 5, 15, 25, and 35 min following presentation of water. Mice were observed for signs of blanching or malaise. None were seen.

*Activity.* The 15 mice were each tested on 2 test days, separated by 4 recovery days, with 2 different Pitressin injections. At the end of 8 hr of water deprivation, mice were placed in the activity drum for 5.5 min with activity measured over the last 5 min of this period. Next, mice were removed, injected with Pitressin, and delayed in a holding compartment for 4.5 min. They were then placed into the activity drum for 5.5 min, with measurement of activity made for the last 5 min of that period.

*Blood pressure.* Each animal was injected with 2 dosages of Pitressin. Systolic blood pressure was measured immediately before the injection and approximately 2.5 min and 35 min after injection. The method involved restraining the animal in a plastic holder, immobilizing the tail and placing the inflatable tail cuff around it.

## RESULTS

*Drinking.* Pitressin injections resulted in temporary inhibition of drinking. This effect is seen in Fig. 1 plotted in terms of cumulative water intakes and also number of animals not yet drinking at various intervals during the 35 min test period. An analysis of variance performed on the 5 min cumulative water intakes showed a significant difference due to injection ($F = 2.63$, $p<0.05$). Comparisons of each injection to the control (0 mU) group by $t$ tests for related means showed that significant ($p<0.05$) depression of drinking was produced by all dosages except the 10 mU. Cumulative water intakes did not differ as a function of injection by 35 min, however, indicating a release from inhibition which is also seen in the steady reduction in the number of animals not yet drinking during the 35 min drinking period.

*Activity.* For the 0, 10, 50 and 200 mU dosage levels there was a trend, but not statistically significant, for activity to decrease following the injection. Following the 800 mU injection, however, activity decreased 60% ($t = 8.26$, $p<0.01$).

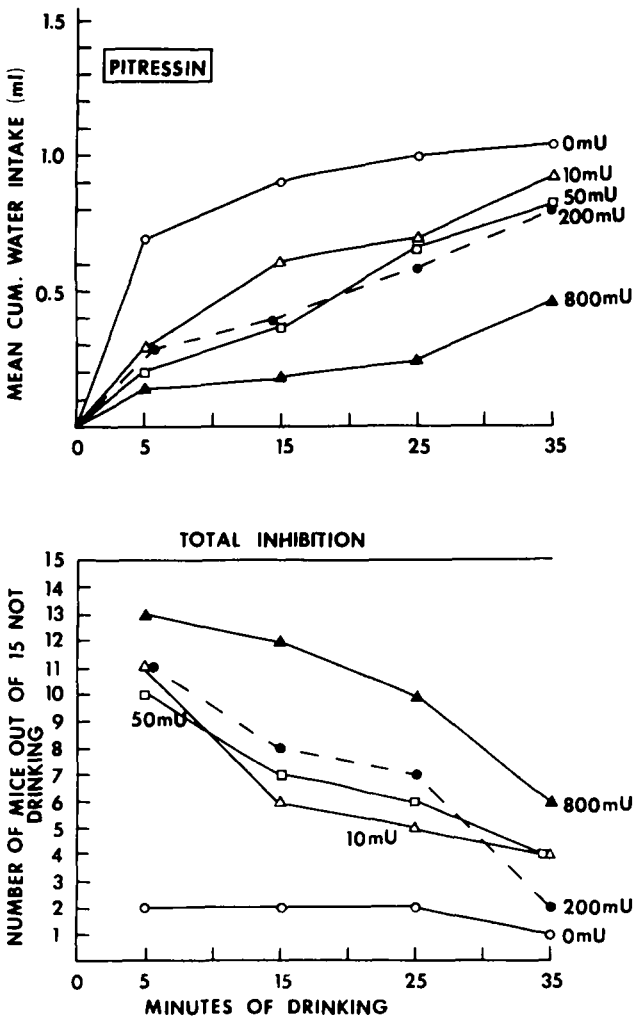


FIG. 1. (Top) Mean cumulative water intakes. Numbers indicate Pitressin dosage. (Bottom) Number of mice out of 15 with no measurable cumulative water intake.

*Blood pressure.* Blood pressure could not be measured following the 800 mU injection because of failure to detect a pulse, possibly because of vasoconstriction. For other injection levels, blood pressure was measurable, but no significant change in blood pressure was noted as a result of the injection.

## DISCUSSION

In the water-deprived SWR/J mice, Pitressin caused only inhibition of drinking. No facilitation was seen, providing no evidence that the abnormally high water intakes of the older, polydipsic female SWR/J mice are due to high production of ADH [14]. The inhibition is clearly transient. In a pilot experiment, injection of 10–50 mU of Pitressin into water-deprived mice produced no inhibition of drinking when water was given 60 min after injection, instead of 5 min after injection.

The physiological basis of the inhibition of drinking is not known. It is probably not dependent upon antidiuretic action on the kidney, because the diabetic mice at time of injection already had a mean weight loss of 13.3%, repre-

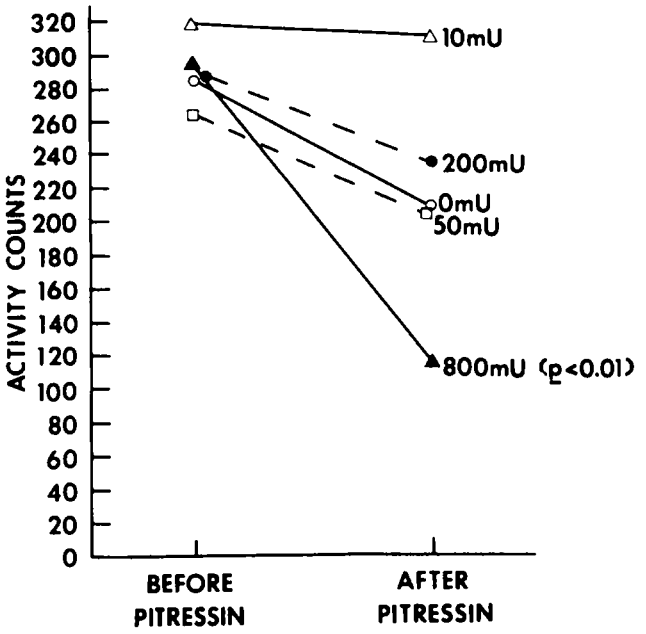


FIG. 2. Activity counts before and after Pitressin injection.

senting a substantial body water loss. Any antidiuresis produced in the 10 min interval between injection and the end of the first 5 min of drinking should be inconsequential.

The inhibition seems to be somewhat specific to drinking rather than a gross pharmacological depression of behavior since general activity was not significantly reduced by Pitressin in the 10–200 mU range. Large Pitressin injections in humans may result in malaise due to the occurrence of tremor, abdominal cramps, nausea, vomiting, vertigo, and anaphalaxis [6].

It is possible that Pitressin produces a rapid reduction of hypovolemia, cell dehydration, or both, which probably occur in the water-deprived mouse. Vasoconstriction could shift the blood from peripheral vessels into the central low-pressure part of circulation thus causing a transient inflation of vascular areas which contain volume receptors, as happens in Pitressin-injected dogs [19]. In the present study, however, no pressor effects were measurable following injections. It is also possible that the injection shifted water from the gut into the extracellular and intracellular compartments [4].

Cell dehydration could be reduced by shifts of electrolytes. Friedman *et al.* [12] found that Pitressin injections in rats caused a transient shift of sodium and water into the cells within the first five min following injection. This is an attractive hypothesis since the time course of Pitressin-induced events in the rat parallel rather well the inhibition of drinking seen in the present study.

A direct action on the nervous system cannot be ruled out. A single injection of Pitressin in rats prevented the extinction of a conditioned avoidance response to shock for at least 72 hr [7], an effect which is most certainly neurally mediated.

Further experiments are needed to verify that the observed inhibition of drinking is due to the action of vasopressin and is not mediated by any impurities in the vasopressin preparation.

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