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BRIEF COMMUNICATION

# Angiotensin Converting Enzyme Inhibitor Captopril Suppresses a Genetic Polydipsic Behavior[1]

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SILVERSTEIN, E. AND J. FRIEDLAND. *Angiotensin converting enzyme inhibitor captopril suppresses a genetic polydipsic behavior.* PHARMACOL BIOCHEM BEHAV **37**(4) 831–833, 1990.—The STR/N inbred mouse is a behavioral mutant that drinks up to four times its body weight in water or normal saline per day when given free access, despite the lack of physiological need. Since angiotensin II (AII) is a powerful elicitor of drinking behavior, we investigated the influence of the angiotensin converting enzyme inhibitor, captopril, on the amount of water consumed by the STR/N mouse. Oral administration of captopril, which inhibits formation of AII (active octapeptide) from AI (precursor decapeptide), resulted in a reduction of 46 to 79% in water consumption of 53 polydipsic STR/N mice, and a 20–42% increase in water consumption of 12 of 13 Swiss/Webster (S/W) normodipsic control mice. These results suggest that the polydipsic behavior of the STR/N mutant may involve mediation by AII and/or another molecule which is also suppressed by captopril, such as another peptide, which, for activation, requires cleavage by a peptidase which is inhibited by captopril.

Behavior Genetic Primary polydipsia Angiotensin converting enzyme Inhibitor Captopril Angiotensin I Angiotensin II

INHERITED polydipsia in the inbred STR/N mouse strain arose following 3-methylcholanthrene treatment. The precise genetic basis of the inherited polydipsia remains to be elucidated (11). The polydipsia appears to be due to an innate thirst, and is not only unnecessary for survival, but even detrimental since males develop hydronephrosis and die prematurely due to polyuria and formation of a urethral plug in most male mice. The STR/N polydipsia is mild at 4–6 weeks of age and increases markedly by 5–6 months. The urine of polydipsic mice is normally quite dilute, but a concentrated urine is excreted in response to acute or chronic water deprivation or administration of exogenous vasopressin. Normally abundant neurosecretory substance (chromalum-hematoxylin stain) and immunoreactive vasopressin (unpublished) is present in axons and cell bodies of the supraoptic nucleus, posterior pituitary and paraventricular region. Mice which had been chronically water-deprived for 15 months since weaning were avidly polydipsic when given water ad lib (12).

The F1 and F2 hybrids from crosses between the polydipsic STR/N mouse strain and the normodipsic DBA/2JN mouse tended to have water intake intermediate between the two strains, but closer to the normodipsic progenitor. Water consumption of both backcrosses tended to be closer to that of the polydipsic strain (11).

The renin-angiotensin system is present peripherally as well as in the brain. Renin and angiotensinogen messenger RNA sequences have been identified in mouse and rat brain, indicating in situ synthesis of renin and angiotensinogen (2). Oral administration of captopril in sufficient dose results in peripheral as well as central inhibition of angiotensin converting enzyme activity (10). To test the hypothesis that AII, a potent elicitor of drinking behavior (3), may be involved in the polydipsia of the STR/N strain, we investigated the effect on the polydipsia of captopril inhibition of angiotensin converting enzyme-catalyzed cleavage of AI to AII (9).

## METHOD

The STR/N (29 male, 24 female, 6–10 months old) and S/W (21 male, 5 months old) mice were housed in plastic cages lined with wood chips in a room maintained at 74 ± 2°F, with a 12-hour

[1]A brief account of this work has been presented (14).

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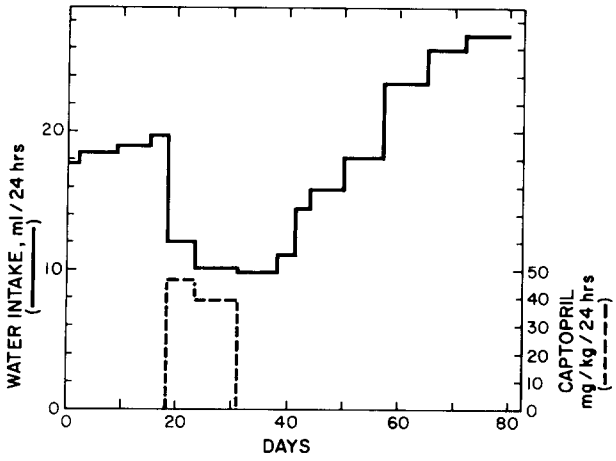


FIG. 1. Decrease in water consumption of a 7-month-old male STR/N mouse during the period of oral administration of captopril at the doses indicated.

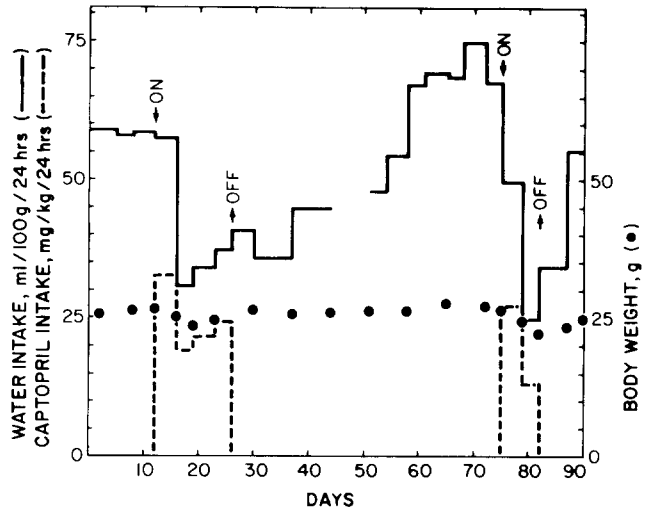


FIG. 2. Decrease in mean water consumption and body weight of five female STR/N polydipsic mice during the period of oral administration of captopril at the doses indicated. "ON" indicates onset and "OFF" signifies cessation of captopril administration.

light-12-hour dark cycle. The diet was Purina laboratory chow pellets with water ad lib. Drinking water was acidified with 0.1 ml of 12.5 N HCl to suppress microorganism contamination and for captopril stability, and was changed twice weekly. Water consumption (volumetrically determined) and body weight were obtained generally every 3 or 4 days. The mean of the body weight at the beginning and the end of each water measurement period was calculated.

The S/W control mice were divided into three groups. The first was given only water to drink. The second was given sufficient captopril in the drinking water for the daily oral administration of 75 mg/kg. For example, for a 32 g mouse with water consumption of 6.4 ml/day, captopril was administered in the drinking water at a concentration of 0.375 mg/ml to achieve a daily dose of 75 mg/kg. The third group was given only water to drink for 9 consecutive days. For the next 5 days sufficient captopril was given in the drinking water for the daily oral administration of 20 mg/kg.

The STR/N mice were administered captopril in the drinking water after and before control periods of water only. A smaller daily target dose of 37.5 mg/kg or less of captopril was used for the STR/N mice, since it was previously found that 75 mg/kg was toxic, resulting in a significant mortality after several days. The variation in daily water intake in the absence of captopril was 0.6% to 13.2% (mean, 6.6%) for STR/N mice in a representative experiment, and 1.8% to 10.3% (mean, 9.7%) for S/W mice in the presence of captopril.

## RESULTS

Oral administration of 12 to 40 mg/kg/day of captopril to STR/N mice resulted in a reduction of 46 to 79% in their water intake. Cessation of captopril administration was followed by recovery of water intake to near initial levels and up to 34% increased levels over the course of several weeks (Figs. 1 and 2). In contrast, 8 S/W normodipsic mice increased their water consumption by 37% in the course of oral administration of 75 mg/kg of captopril (Fig. 3). Oral administration of 20 mg/kg/day of captopril increased the water consumption of 4 of 5 S/W male mice by 20 to 42% ($p<0.05$ in 3 of 5) (Table 1). Both STR/N and S/W mice tend to lose at least 5% of their body weight on captopril (Figs. 2 and 3). The water intake and weight of mice on captopril were significantly different from those of the same strain not on captopril by the paired $t$-test (Figs. 1–3) ($p<0.05$).

## DISCUSSION

The decrease in the water intake of STR/N mice in response to oral captopril was not due to a possibly unpleasant taste of captopril-containing water since parenterally administered captopril (peripherally and centrally) also suppressed water consumption (7). The results suggests the possibility that increase in the AII-bound form of AII receptor, presumably in the brain, may be the signal driving the polydipsic behavior of the STR/N mouse, either through increase in AII concentration or increased receptor affinity for AII. Recent in vitro neurophysiological studies on thin brain slice preparations suggest that AII receptors of neurons in the subfornical organ and the AV3V region of STR/N mice do not

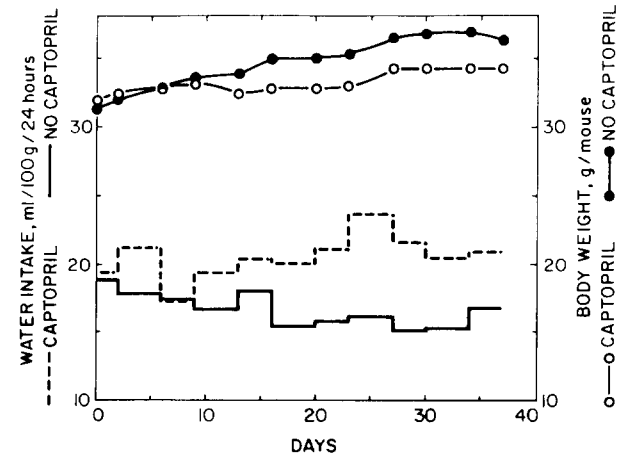


FIG. 3. Increase in mean water consumption and decrease in mean body weight of 4 male normodipsic Swiss/Webster mice during the period of oral administration of 75 mg/kg/24 hr of captopril, in comparison to 4 male Swiss/Webster mice not receiving captopril.

TABLE 1

EFFECT OF CAPTOPRIL ON WATER CONSUMPTION OF S/W MICE

| Mouse No. | Mean Daily Water Intake ± SEM*, ml No Captopril | Captopril PO 20 mg/kg/Day | |
|---|---|---|---|
| 1 | 11.1 ± 0.538 | 13.3 ± 0.347 | $p<0.02$ |
| 2 | 9.58 ± 1.07 | 11.8 ± 4.27 | $p<0.2$ |
| 3 | 10.0 ± 0.190 | 12.2 ± 0.303 | $p<10^{-5}$ |
| 4 | 10.8 ± 0.125 | 15.3 ± 0.619 | $p<10^{-6}$ |
| 5 | 12.1 ± 0.343 | 11.7 ± 0.690 | $p<0.7$ |

*Standard error of the mean.

have increased affinity for AII in comparison with S/W controls (7).

Since opioid inhibitors also suppress the polydipsia (13), the mechanism of the polydipsia may involve interaction of AII and opioids. Alternatively, an opioid mechanism may be involved, and captopril may suppress the polydipsia by inhibition of the proteolytic processing of opioid percursor peptide(s) (1,8).

Genetically determined polydipsia in the STR/N mouse appears to be a useful model for the study of the molecular mechanism of drinking behavior.

The cause of the decrease in body weight on captopril administration in both normodipsic and polydipsic mice is not known. The weight loss suggests possible inhibition of appetite and food consumption by captopril through suppression of AII formation or by another mechanism, presumably involving inhibition of proteolytic cleavage. Alternatively, a more complex interaction of effects may be involved in the decrease in body weight. A significant reduction in food intake in the rat in response to captopril administration has been reported (6). In man, a 2–4% incidence of loss or diminution of taste perception associated with weight loss has been noted (5).

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