CLIN. AND EXPER.-THEORY AND PRACTICE, A6(10&11), 2107-2111 (1984)

ROLE OF ANGIOTENSIN II(AII) RECEPTORS IN DISCRETE RAT BRAIN AREAS AND POSTERIOR PITUITARY

J.M. Saavedra, M. Kadekaro, A. Israel, M. Niwa, H. Holcomb, P. Gross and L. Sokoloff.
Section on Clinical Psychopharmacology, Laboratory of Clinical Science, NIMH, Bethesda, MD 20205, USA

INTRODUCTION

Blood-borne angiotensin II (AII) stimulates drinking, increases blood pressure and releases pituitary hormones (1), effects mediated, at least partially, through stimulation of AII receptors in circumventricular organs (2). We tried to determine whether AII could modulate the metabolic activity of its target sites in the rat brain, and whether any correlation could be found between such a modulation and the number of AII receptors in a particular brain structure.

MATERIAL AND METHODS

Four month-old male Sprague Dawley (SD) and Long Evans (LE) controls, and homozygous Brattleboro (DI) rats were obtained from NIH. Groups of 4 to 10 rats were water deprived (5 days for SD, 16 hr for LE and DI). One group of DI rats was injected with vasopressin (Pitressin, Parke Davis) 500 mU/100 g body weight, daily for 7 days. Glucose utilization was determined by the [^{14}C]-deoxyglucose autoradiographic method (3, 4). Angiotensin receptors were quantitated after incubation with ^{125}I-[Sar^{1}]-AII, autoradiography, computerized densitometry (4, 5) and comparisons with ^{125}I standards (6).

RESULTS

In the subfornical organ (SFO) DI rats presented enhanced glucose utilization when compared to SD or LE controls (Figure 1). Vasopressin substitution reduced the increased glucose utilization in DI rats to levels no different from those in control rats (Figure 1). Water deprivation of SD rats for 5 days increased glucose utilization by 62%. When water deprived for 16 hr, LE rats increased their glucose utilization by 19%, and DI rats by 35% (Fi-

 0730-0077/84/0610-2107$3.50/0

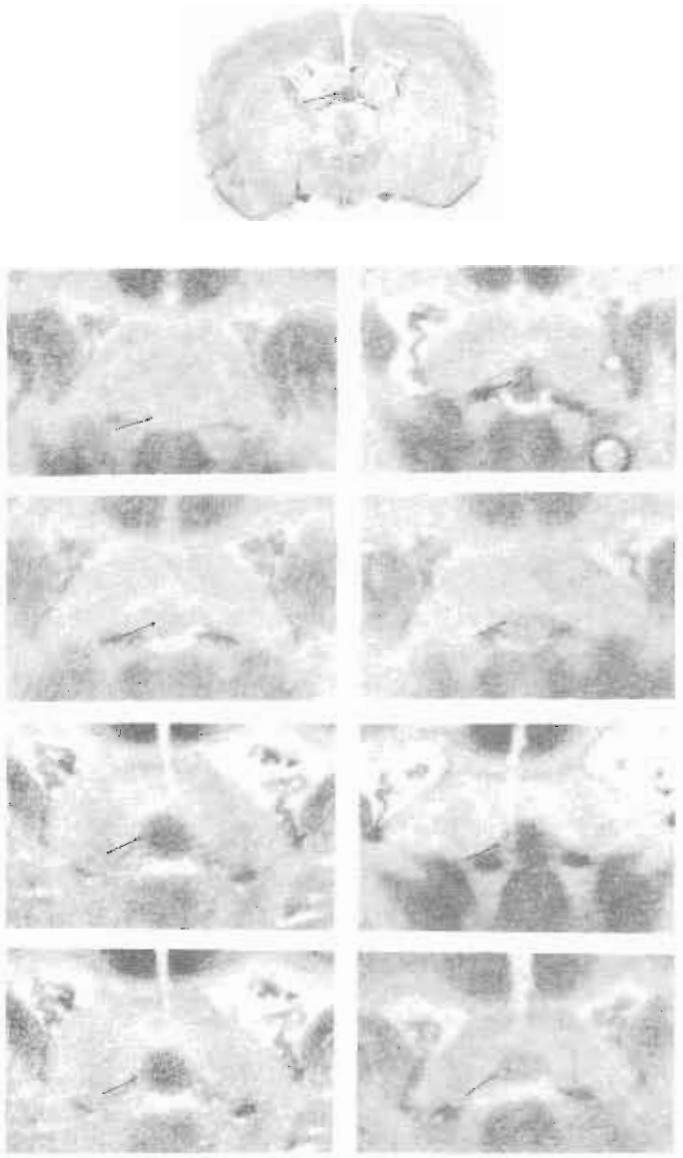

FIGURE 1. GLUCOSE UTILIZATION IN THE SUBFORNICAL ORGAN IN WATER-DEPRIVED BRATTLEBORO AND CONTROL RATS. Arrows point to the subfornical organ. From uppper to lower panels: Nissl stain. SD rats: control (left) 40 ± 3; water deprivation (right) 65 ± 2*. LE: control (left) 48 ± 2; water deprivation (right) 57 ± 2*. DI: control (left) 69 ± 5**; water deprivation (right) 93 ± 5*. DI: control (left) 69 ± 3; vasopressin replacement (right) 53 ± 4)***. Numbers are umol/100g/min, X ± S.E.M. *p<0.05, water deprived vs control. **p<0.05, DI vs control LE or SD. ***p<0.05, DI vasopressin treated vs DI.

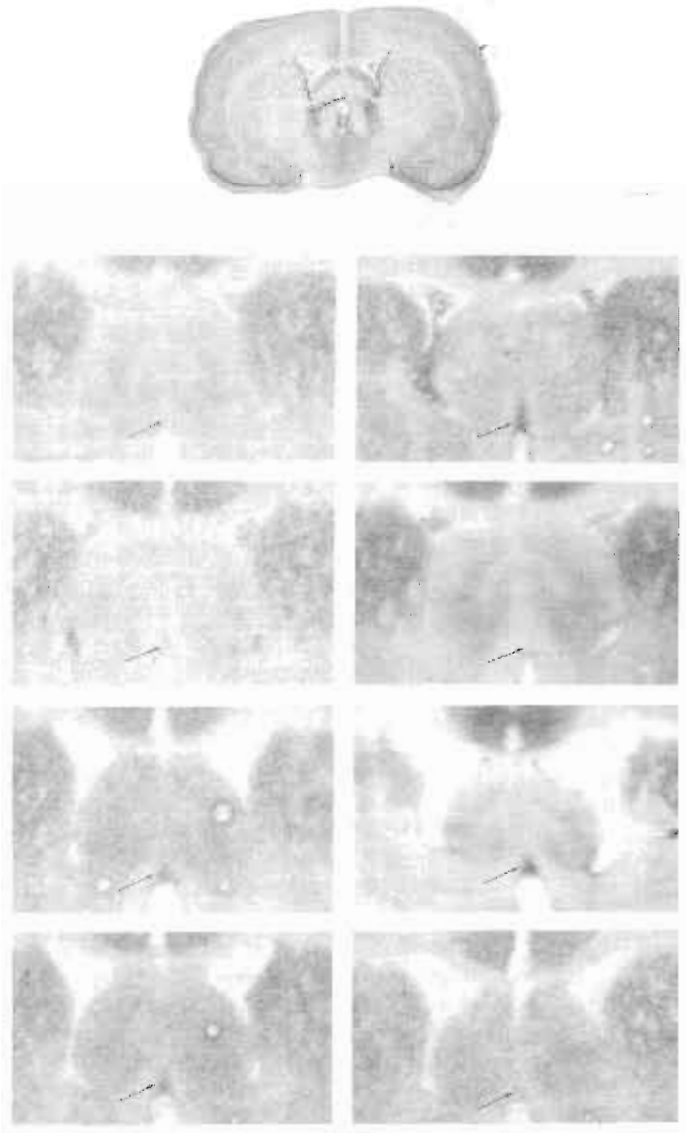

FIGURE 2. GLUCOSE UTILIZATION IN THE NUCLEUS SEPTALIS TRIANGULARIS IN WATER-DEPRIVED BRATTLEBORO AND CONTROL RATS. Arrows point to the nucleus septalis triangularis. Panels are from the groups as in Figure 1. SD: control 45 ± 3; water deprived 83 ± 2 *; LE: control 49 ± 4; water deprived 63 ± 5.* DI: control 68 ± 5**; water deprived 107 ± 6*. DI: control: 68 ± 5**; vasopressin replacement 50 ± 3***. Numbers are µmol/100g/min, X ± S.E.M. *p<0.05, water deprived vs. control. **p<0.05, DI vs control LE or SD. ***p<0.05, DI vassopressin treated vs DI.

gure 1). Similar changes in glucose utilization between DI rats and controls, after dehydration and after vasopressin occurred in the nucleus septalis triangularis (Figure 2).

Glucose utilization was also higher in posterior pituitary of DI rats when compared to LE controls. Water deprivation increased glucose utilization in posterior pituitary of both LE and DI. (LE: 41 ± 2 and 61 ± 10 *; DI: 83 ± 5 ** and 132 ± 12 * μmol/100g/min; * $p<0.05$ dehydrated vs control; ** $p<0.05$ DI vs LE).

High density of single class, high affinity AII receptors were detected in the SFO of SD control rats (Ka: 1.5 $10^9 M^{-1}$, Bmax 265 fmol/mg protein. In contrast, very few AII receptors were detected in posterior pituitary of SD rats (results not shown).

DISCUSSION

Acute or chronic dehydration increases glucose utilization specifically in the SFO. DI rats, unable to synthesize vasopressin, are chronically dehydrated (7) and are more susceptible to acute dehydration, increasing the glucose utilization substantially more than controls. In DI rats, this metabolic change can be corrected by hormonal (vasopressin) substitution.

Similar metabolic changes in DI rats and in normal, water deprived animals are detected in the nucleus septalis triangularis, a structure anatomically connected to the SFO-neurohypophyseal pathway (8). These discrete alterations in brain glucose utilization are probably due to stimulation of the SFO by blood-borne AII. Blockade of peripheral AII formation by Captopril reverses the increased glucose utilization in both the SFO and the nucleus septalis triangularis, and AII infusion to normal rats increases glucose utilization in the same structures, a process prevented by the AII antagonist saralasin (Gross, Kadekaro, Andrews, Sokoloff and Saavedra, submitted).

Similar changes in glucose utilization occur in the posterior pituitary of DI rats, in normal, water-deprived animals, and after AII infusion to normal rats, probably indicating AII-mediated increased metabolic activity of the neurohypophyseal axis during dehydration (9). However, very few AII receptors occur in the posterior pituitary, whereas high affinity AII receptors are abundant in the SFO (10). These observations suggest that blood-borne AII activates specific AII receptors in the SFO, resulting in the metabolic activation of this structure and of the pathway connecting the SFO to the terminal neurohypophyseal axons (8), with the end result of increased vasopressin release to the circulation.

REFERENCES

1. Fitzsimons JT, Angiotensin stimulation of the central nervous system. Rev. Physiol. Biochem. Pharmacol. (1980) 87, 117-167.
2. Simpson JB, The circumventricular organs and the central action of angiotensin. Neuroendocrinology (1981) 32, 248-256.

3. Sokoloff L, Revich M, Kennedy C, Des Rosiers MH, Patlak CS, Pettigrew KD, Sakurada O, Shinohara M, The [^{14}C]-deoxyglucose method for the measurement of local cerebral glucose utilization: theory, procedure, and normal values in the conscious and anesthetized albino rat. J. Neurochem. (1977) 28, 897-916.
4. Goochee C, Rasband W, Sokoloff L, Computerized densitometry and color coding of [^{14}C]-deoxyglucose autoradiographs. Ann. Neurol. (1980) 7, 359-370.
5. Unnerstall JR, Niehoff DL, Kuhar MJ, Palacios JM, Quantitative receptors autoradiography using [^{3}H]Ultrofilm: application to multiple benzodiazepine receptors. J. Neuroscience Methods (1982) 6, 59-73.
6. Israel A, Correa FMA, Niwa M, Saavedra JM, Quantitative determination of angiotensin II binding sites in rat brain and pituitary gland by autoradiography. Brain Research (in press).
7. Valtin H, Schroeder HH, Familial hypothalamic diabetes insipidus in rats (Brattleboro strain). Am. J. Physiol. (1964) 206, 425-430.
8. Miselis RR, The efferent projections of the subfornical organ of the rat: a circumventricular organ within a neural network subserving water balance. Brain Research (1981) 230, 1-23.
9. Kadekaro M, Gross P, Sokoloff L, Holcomb HH, Saavedra JM, Elevated glucose utilization in subfornical organ and pituitary neural lobe of the Brattleboro rat. Brain Research (1983) 275, 189-193.
10. Israel A, Correa FMA, Niwa M, Saavedra JM, Quantitative measurement of angiotensin II (AII) receptors in discrete regions of rat brain, adrenal and pituitary gland by autoradiography. (This volume).