Central infusion of aldosterone synthase inhibitor prevents sympathetic hyperactivity and hypertension by central Na\textsuperscript{+} in Wistar rats

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Huang BS, White RA, Ahmad M, Jeng AY, Leenen FHH. Central infusion of aldosterone synthase inhibitor prevents sympathetic hyperactivity and hypertension by central Na\textsuperscript{+} in Wistar rats. Am J Physiol Regul Integr Comp Physiol 295: R166–R172, 2008. First published May 21, 2008; doi:10.1152/ajpregu.90352.2008.—In Wistar rats, increasing cerebrospinal fluid (CSF) Na\textsuperscript{+} concentration ([Na\textsuperscript{+}]) by intracerebroventricular (ICV) infusion of hypertonic saline causes sympathetic hyperactivity and hypertension that can be prevented by blockade of brain mineralocorticoid receptors (MR). To assess the role of aldosterone produced locally in the brain in the activation of MR in the central nervous system (CNS), Wistar rats were infused ICV with artificial CSF (aCSF), Na\textsuperscript{+}-rich (800 mmol/l) aCSF, aCSF plus the aldosterone synthase inhibitor FAD286 (100 \textmu g-kg\textsuperscript{-1}-day\textsuperscript{-1}), or Na\textsuperscript{+}-rich aCSF plus FAD286. After 2 wk of infusion, rats treated with Na\textsuperscript{+}-rich aCSF exhibited significant increases in aldosterone and corticosterone content in the hypothalamus but not in the hippocampus, as well as increases in resting blood pressure (BP) and sympathoexcitatory responses to air stress, and impairment of arterial baroreflex function. Concomitant ICV infusion of FAD286 prevented the Na\textsuperscript{+}-induced increase in hypothalamic aldosterone but not corticosterone and prevented most of the increases in resting BP and sympathoexcitatory and pressor responses to air stress and the baroreflex impairment. FAD286 had no effects in rats infused with ICV aCSF. In another set of rats, 24-h BP and heart rate were recorded via telemetry before and during a 14-day ICV infusion of Na\textsuperscript{+}-rich aCSF with or without FAD286. Na\textsuperscript{+}-rich aCSF without FAD286 caused sustained increases (~10 mmHg) in resting mean arterial pressure that were absent in the rats treated with FAD286. These data suggest that in Wistar rats, an increase in CSF [Na\textsuperscript{+}] may increase the biosynthesis of corticosterone and aldosterone in the hypothalamus, and mainly aldosterone activates MR in the CNS leading to sympathetic hyperactivity and hypertension.

brain sodium; brain steroids; mineralocorticoid receptor; cytochrome P-450 aldosterone synthase; hypothalamus; sympathoexcitation; diurnal variation

If so, specifically increasing CSF [Na\textsuperscript{+}] or aldosterone should reproduce this high-salt diet-induced phenotype. Indeed, in normotensive rats chronic intracerebroventricular (ICV) infusion of Na\textsuperscript{+}-rich artificial CSF (aCSF) increases aldosterone content in the hypothalamus (11) and causes sympathetic hyperactivity and hypertension (15, 16, 18), which can be prevented by CNS blockade of MR with ICV spironolactone (11). Similarly, ICV infusion of aldosterone causes sympathetic hyperactivity and hypertension (17, 28). Enzymes involved in steroid biosynthesis are present in the CNS (21). However, it is still doubtful whether the brain can produce aldosterone in biologically active amounts (7). Changes in content may reflect changes in uptake or metabolism rather than local changes in synthesis. Moreover, it is possible that ICV infusion of Na\textsuperscript{+}-rich aCSF also increases hypothalamic corticosterone. Both corticosterone and aldosterone can act as agonists contributing to MR stimulation in the CNS. Aldosterone and corticosterone bind MR with equal affinity (1), but the presence of the corticosterone-inactivating enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD-2) enhances aldosterone selectivity of the MR in brain regions such as the paraventricular nucleus of the hypothalamus (28). A decrease in 11β-HSD-2 activity also may lead to activation of MR in the CNS and thereby affect cardiovascular regulation (28).

In the present study, we evaluated the effects of a chronic increase in CSF [Na\textsuperscript{+}] on hypothalamic aldosterone and corticosterone content and the specific role of locally produced aldosterone in sympathoexcitation and hypertension by ICV infusion of the cytochrome P-450 aldosterone synthase (CYP11B2) inhibitor FAD286 (5). Wistar rats were treated for 2 wk with an ICV infusion of Na\textsuperscript{+}-rich CSF or aCSF with or without concomitant ICV infusion of FAD286. Blood pressure (BP) and heart rate (HR) were measured either by telemetry throughout or by intra-arterial catheter after the 2-wk infusion, followed by assessment of sympathoexcitatory and pressor responses to air stress and arterial baroreflex control of renal sympathetic nerve activity (RSNA) and HR. Aldosterone and corticosterone content were measured in the hypothalamus and hippocampus as well as in plasma to assess possible peripheral changes contributing to central changes. The results indicate that a small increase in CSF [Na\textsuperscript{+}] increases both corticosterone and aldosterone in the hypothalamus but not in the plasma, suggesting that an increase in CSF [Na\textsuperscript{+}] activates enzymes in the steroid biosynthetic pathway in the CNS. The increase in aldosterone appears to play a functional role in stimulation of MR in the CNS and thereby in sympathetic hyperactivity and hypertension.

IN DAHL SALT-SENSITIVE (S) rats, high salt intake causes a persistent increase in cerebrospinal fluid (CSF) Na\textsuperscript{+} concentration ([Na\textsuperscript{+}]) (14, 23) and increases aldosterone content in the hypothalamus (12). Central nervous system (CNS) blockade of aldosterone synthesis (12), or of mineralocorticoid receptors (MR) (8, 12, 24), prevents the high-salt-induced sympathetic hyperactivity and hypertension in Dahl S rats. We postulated that in Dahl S rats on high salt enhanced Na\textsuperscript{+} entry from blood to brain interstitium activates local aldosterone biosynthesis and release, and thereby activates central pathways resulting in sympathetic hyperactivity and hypertension.

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METHODS

Male Wistar rats weighing 200–250 g (Charles River, Montreal, QC, Canada) were housed in a climatized room on a 12:12-h light-dark cycle at constant room temperature and humidity and given standard laboratory chow (120 μmol Na+/g) and tap water ad libitum. The study was carried out in accordance with the guidelines of the Canadian Council on Animal Care, which conform to National Institutes of Health guidelines, and was approved by the University of Ottawa Animal Care Committee.

Protocol 1. After a 1-wk acclimatization, under isoflurane inhalation a stainless steel cannula was implanted into the left lateral cerebral ventricle and fixed to the skull of the rat with acrylic cement. A stainless steel cannula was implanted into the left lateral cerebral ventricle and fixed to the skull of the rat with acrylic cement. Intravenous (5–100 μg/kg, 10 min apart, with an air jet stream (1–1.5 lb/in.2) directed to the face). Total activity (13).

Each rat was killed at the end of the study and subtracted from the background noise on the RSNA recordings was determined after a 10-min period. The cannula was right-angled with the upper end connected to an osmotic minipump (model 2ML2, Alza, Palo Alto, CA) for chronic ICV infusion at 5 μl/h for 14 days.

The pump was filled with aCSF or aCSF containing 800 mmol/l Na+ (Na+-rich aCSF) alone or combined with FAD286 (100 μg·kg·day−1) (4 groups in total, n = 7 or 8/group) and implanted subcutaneously on the back of the rat. ICV infusion of the Na+-rich aCSF at this rate for 2 wk increases CSF Na+[1] by 4.5–5 mmol/l (15). FAD286 is a single (+)-enantiomer. FAD286 hydrogen tartrate (Novartis Institutes for BioMedical Research) was used because it is soluble in aCSF. Each 1.67 mg of FAD286 hydrogen tartrate provides 1 mg of FAD286 free base, and the amount of the drug in the pumps was adjusted accordingly. The rate of ICV infusion of FAD286 was based on previous studies (12). The composition of the aCSF was (in mmol/l) 121 NaCl, 3.4 KCl, 1.2 MgCl2, 0.6 NaH2PO4, 29 NaHCO3, and 3.4 glucose. The pH was 7.4, and osmolality was 296 mosmol/kg H2O. Rats were trained to stay for 30 min in a small testing cage three times per week during the 2-wk infusion period.

At the end of the 14-day infusion, rats were anesthetized with isoflurane, and PE-10 (fused to PE-50) catheters filled with heparinized saline were inserted in the right femoral vein and in the abdominal aorta through the right femoral arterial. Via a left flank incision, a pair of silver electrodes was attached to and glued around a segment of the renal nerve (13). The catheters and electrodes were tunneled to the back of the neck. About 4–5 h later, after recovery from the anesthesia the rat was placed in a testing cage, the intra-arterial catheter was connected to a transducer, and BP and HR were recorded through a polygraph (model 7E, Grass Instrument, Quincy, MA) and a Grass 7P44 tachograph. The electrodes were linked to a Grass PS11 band-pass amplifier. And the amplified RSNA signals were channeled to a rectifying voltage integrator (Grass model 7P10) and recorded through the polygraph. The RSNA signals (mV), together with BP and HR, were also fed into an online computer equipped with a Grass data acquisition and analysis program (Polyview 2.0). The background noise on the RSNA recordings was determined after each rat was killed at the end of the study and subtracted from the total activity (13).

After a 30-min rest, RSNA, BP, and HR were recorded for 5 min. A standardized air jet stress was then applied for two 30-s intervals, 10 min apart, with an air jet stream (1–1.5 lb/in.2) directed to the face of the rat (13). Peak increases in RSNA, BP, and HR from the resting values measured 1 min before each stress were recorded, and the mean of the two peak responses was used for statistical analysis. Twenty minutes after the responses to air stress had subsided, phenylephrine in 5% dextrose was infused intravenously at increasing rates (5–50 μg·kg−1·min−1) to achieve a ramp increase in BP up to 50 mmHg over 0.5–1 min. Twenty minutes after BP, RSNA, and HR had returned to baseline, sodium nitroprusside in 5% dextrose was infused intravenously (5–100 μg·kg−1·min−1) to induce a ramp decrease in BP by 50 mmHg over 0.5–1 min. The infusion rates were <0.08 ml/min in both cases. Responses of RSNA were expressed as percentage of resting values. To evaluate arterial baroreflex function, changes in RSNA/HR (ΔRSNA/ΔHR) in response to changes in mean arterial pressure (MAP) were analyzed as a logistic model, with the equation ΔRSNA/ΔHR = P1 + P3[1 + e(−(MAP − P2))], where P1 is lower ΔRSNA/ΔHR plateau, P2 is ΔRSNA/ΔHR range, P3 is a curvature coefficient, and P4 is MAP50, i.e., the MAP at one-half the ΔRSNA/ΔHR range. The maximum slope (gain) equals to −P2 × P3/P4 (4).

About 30 min after the assessment of baroreflex function, 3 ml of blood was collected from the arterial line into ice-chilled tubes for aldosterone, corticosterone, and ANG II assays. The rats were then killed with an overdose of intravenous pentobarbital, and the whole brain was removed and frozen quickly in dry ice and stored at −80°C. The whole hypothalamus and hippocampus were dissected frozen, on ice, according to Glowinski and Iversen (6) and thawed only when homogenized for the corticosterone and aldosterone assays.

Plasma and brain aldosterone were measured by radioimmunoassay (RIA) as described previously (11, 19). Briefly, plasma was applied to preconditioned C18 cartridges and aldosterone was eluted with 80% methanol after prewashing with 12% methanol. The eluates were dried in a vacuum concentrator and then redissolved in PBS containing 0.5% BSA for the RIA. Aldosterone antiserum (ICN Pharmaceuticals no. 07-108226) and 125I-labeled aldosterone (ICN Pharmaceuticals no. 07-108226) were added, and the tubes were incubated 16–24 h at 4°C. After separation with dextran-coated charcoal, the supernatant was counted with a Canberra-Packard AutoGamma counter. For the assay of hypothalamic aldosterone, the tissue was first homogenized in 100% methanol. After centrifugation, the supernatant was dried in a vacuum concentrator. The residues were redissolved in 0.1% trifluoroacetic acid and centrifuged, and the supernatants were applied to preconditioned cartridges and assayed as described for plasma. For the standard curve, the lowest detectable value was 0.5 pg per tube. Since the average weight of hypothalamic tissue extracted was 80–90 mg and the amount put into each RIA tube was ~14 mg, the sensitivity for hypothalamic aldosterone was 0.5/14 = 0.035 pg/mg. Observed levels of hypothalamic aldosterone (>0.25 pg/mg) were much higher than this level. The intra-assay variation was 7%, and all samples from the experiment were done in one assay. The recovery, i.e., spiking of plasma or tissue with known concentrations of aldosterone, was ±88%. Cross-reactivities were 0.03% and 0.14% for corticosterone and 11-deoxycorticosterone (DOC), respectively. Plasma and tissue corticosterone were determined with a corticosterone-125I RIA kit (MP Biomedicals, product no. 07-120103).

Plasma ANG II concentrations were measured by RIA after extraction on Sep-Pak C18 cartridges and separation by HPLC (20).

Protocol 2. In three groups of Wistar rats on regular salt, under isoflurane anesthesia a telemeter probe (DSI model TA11PA-C40) was placed into the abdominal cavity and secured to the ventral abdominal wall with the catheter inserted into the abdominal aorta (10). The telemeter signal was obtained with an analog adapter and data acquisition system that was set to calculate and store the mean values of resting BP and HR during a 3-s interval over a 1-min period each hour. Continuous recordings were started 3 days after the probe implantation. After 3 days of control recordings, under isoflurane anesthesia a stainless steel cannula was implanted into the left lateral cerebral ventricle as described above. The cannula was connected to an osmotic minipump (model 2ML2) and filled with either aCSF (n = 4) or Na+-rich aCSF with (n = 8) or without (n = 8) FAD286 (100 μg·kg−1·day−1). The rats were returned to their original cages, and telemetry recordings continued for an additional 14 days.

Statistical analysis. For data in protocol 1, a two-way ANOVA was performed to determine the effects of ICV infusion of Na+-rich aCSF and FAD286 on the various parameters. When the F values were significant, a Duncan multirange test followed to locate the significant differences. For comparisons of the responses to the ICV infusions in protocol 2, a one-way repeated-measures ANOVA was performed. When the F values were significant for main effect, a Duncan’s test was performed for multiple comparisons. To evaluate diurnal differences of MAP and HR, average telemetry data during nighttime (12-h
lights on) and nighttime (12-h lights off) were analyzed with paired \( t \)-test. The relationship between plasma and hypothalamic aldosterone levels was analyzed by Pearson correlation. Statistical significance for all tests was defined as \( P < 0.05 \).

## RESULTS

### Brain and plasma aldosterone and corticosterone

ICV infusion of Na\(^+\)-rich aCSF significantly increased hypothalamic aldosterone by 85% and corticosterone by 65% (Fig. 1). ICV infusion of FAD286 prevented the increase in hypothalamic aldosterone but not corticosterone. FAD286 had no effects on hypothalamic aldosterone and corticosterone in rats infused with ICV aCSF (Fig. 1). Infusion of Na\(^+\)-rich aCSF alone or combined with FAD286 did not change aldosterone and corticosterone content in the hippocampus and in plasma (Table 1). There was no correlation between plasma aldosterone and hypothalamic aldosterone levels either across the four groups of rats or within each of the four groups. Changes in plasma ANG II after ICV infusion of Na\(^+\)-rich aCSF were not significant.

#### Blood pressure

After 2 wk of ICV infusion, Na\(^+\)-rich aCSF increased resting MAP by \( \sim 15 \) mmHg compared with aCSF control, as measured by intra-aortal catheter (Table 1). MAP increased significantly less in rats with ICV Na\(^+\)-rich aCSF plus FAD286 but was still higher than in rats with ICV aCSF. FAD286 had no effects on MAP in rats treated with ICV aCSF (Table 1). HR tended to be higher in rats treated with ICV Na\(^+\)-rich aCSF alone compared with others.

#### 24-h Blood pressure

The average 24-h baseline MAP was \( \sim 95 \) mmHg. In rats with ICV infusion of aCSF, MAP did not change and remained at baseline levels during the 14 days of infusion. MAP increased significantly by 9 mmHg on day 1 of ICV infusion with Na\(^+\)-rich aCSF (Fig. 2) and remained around this level for the following 14 days. In rats treated with Na\(^+\)-rich aCSF plus FAD286, MAP similarly increased on day 1 but then started to decrease on day 2, returning to preinfusion levels on days 3–4, and remaining at this control level for the rest of the infusion. The profiles of changes in systolic and diastolic BP were similar in three groups of rats (not shown). Before ICV infusion of Na\(^+\)-rich aCSF, MAP was \( \sim 5 \) mmHg higher in the night phase versus the day phase. On day 1 of the infusion, this difference in MAP significantly increased in groups treated with Na\(^+\)-rich aCSF but not in groups treated with aCSF (Fig. 3). The larger diurnal difference in MAP persisted in rats treated with Na\(^+\)-rich aCSF but normalized again in rats treated with Na\(^+\)-rich aCSF plus FAD286 from day 4 of the infusion (Fig. 3).

On day 1 of ICV infusion, average HR was increased significantly by 30–40 beats/min in rats treated with Na\(^+\)-rich aCSF and by \( \sim 20 \) beats/min in rats treated with aCSF (\( P = 0.1 \)). In all groups, HR started to decrease toward control levels on day 2 and had returned to control levels on day 4 (Fig. 3). HR showed a modest \( (\sim 35 \) beats/min) diurnal variation, which was not affected by either Na\(^+\)-rich aCSF or aCSF (data not shown).

#### Sympathetic reactivity

ICV infusion of Na\(^+\)-rich aCSF increased peak excitatory responses of RSNA, MAP, and HR to air stress by 85–125% (Fig. 4). ICV FAD286 prevented most of the enhancement in RSNA, BP, and HR responses to air stress. ICV FAD286 had no effects on RSNA, MAP, and HR responses to air stress in rats treated with aCSF.

After 2 wk of ICV infusion of Na\(^+\)-rich aCSF, baroreflex curves for RSNA or HR in relationship to changes in MAP were less steep, associated with significantly lower maximal slope and ranges (Fig. 5), consistent with impaired baroreflex function. These changes were prevented by ICV FAD286. ICV FAD286 had no effects on baroreflex function in rats treated with ICV aCSF.

### DISCUSSION

There are two major findings in the present study. First, in Wistar rats a small increase in CSF [Na\(^+\)] by ICV infusion of Na\(^+\)-rich aCSF increases both aldosterone and corticosterone content in the hypothalamus, but not in the hippocampus or blood. Second, ICV infusion of an aldosterone synthase inhibitor prevents the increase in hypothalamic aldosterone, but not corticosterone, induced by ICV infusion of Na\(^+\)-rich aCSF, and it substantially attenuates sympathetic hyperreactivity, impairment of arterial baroreflex function, and hypertension.

Enzymes involved in steroid biosynthesis are present in the CNS (21), and there is experimental evidence that the rat brain has the enzymatic machinery for steroidogenesis and can synthesize both corticosterone and aldosterone (9). In rats,
cytochrome P-450 11β-hydroxylase (CYP11B1) converts DOC to corticosterone and cytochrome P-450 aldosterone synthase (CYP11B2) catalyzes the steps between DOC and aldosterone (25). The brain is a major extra-adrenal site of CYP11B1 and CYP11B2, and their genes are expressed in several brain areas including the hypothalamus (9, 26). To date, no studies have reported the protein levels or activities of these enzymes in the rat brain. In the hypothalamus of rats, CYP11B2 mRNA expression levels are about 1/10th of those in the adrenal gland and CYP11B1 mRNA levels about 1/1,000th (26). Expression in specific nuclei has not yet been assessed, and the actual expression as well as enzyme activities in specific nuclei may be higher than those observed in the whole hypothalamus. In the present study, tissue levels of corticosterone and aldosterone in the hypothalamus were similar to those reported by others (7, 27). ICV infusion of Na⁺-rich aCSF increased hypothalamic corticosterone by 65% and aldosterone by 85% but had no effects on the content of either steroid in plasma or the hippocampus. These nonparallel changes in hypothalamic and plasma steroid levels suggest that a small increase of [Na⁺] in the brain may increase activities of both CYP11B1 and CYP11B2, or of other enzymes that catalyze rate-limiting step(s) of steroidogenesis in the CNS such as the cholesterol side chain cleavage enzyme CYP11A.

However, actual synthesis was not measured in the present study, and it is possible that increases in content may be due to a decrease in steroid metabolism or increased uptake. Local
infusion of an aldosterone synthase inhibitor distinguishes between the effects of Na$^+$ on local synthesis and possible effects on uptake or metabolism. In the present study, ICV infusion of the aldosterone synthase inhibitor prevented the increase in hypothalamic aldosterone, suggesting that the Na$^+$-rich aCSF-induced increase in aldosterone content is indeed likely a result of increased aldosterone synthesis locally in the brain rather than increased uptake. Further studies are needed to assess how and in which specific brain nuclei/regions Na$^+$ may activate steroiogenesis. The Na$^+$-rich aCSF increased aldosterone content in the hypothalamus but not in the hippocampus, indicating that this effect of Na$^+$ is not a generalized phenomenon in the brain but is region specific. High salt intake, which leads to transient increases in plasma [Na$^+$], decreases CYP11B2 expression and aldosterone synthesis in the adrenal gland (26). Further studies are clearly needed to address the cellular and molecular pathways mediating the stimulatory effects of Na$^+$ on steroid biosynthesis in the CNS.

ICV infusion of FAD286 prevented the Na$^+$-induced increase in hypothalamic aldosterone, but it did not bring levels lower than those in control rats and had no effects on aldosterone levels in rats treated with ICV aCSF. It appears that the basal amount of aldosterone in the hypothalamus mainly reflects uptake of aldosterone of peripheral (adrenal) origin (7), which is not affected by local inhibition of aldosterone synthase. Plasma aldosterone and corticosterone remained similar which is not affected by local inhibition of aldosterone synthase inhibitor were largely similar to those of an MR blocker (11), indicating that in the present experimental paradigm corticosterone exhibited only minimal agonistic activity.

As measured by telemetry, on day 1 of ICV infusion of Na$^+$-rich aCSF resting BP elevated rapidly and to the same extent in rats treated with Na$^+$-rich aCSF with and without FAD286. BP stayed at high levels for the remaining 13 days in the rats without FAD286 treatment, but in rats treated with FAD286 BP started declining on day 2 and returned to control levels on day 4. Since this rapid increase in BP on day 1 was absent in rats treated with ICV infusion of aCSF, it is possible that Na$^+$-rich aCSF first increases release of existing aldosterone, which would not be affected by an aldosterone synthase activator.
thase inhibitor, and the subsequent pressor effects depend on newly synthesized aldosterone. Alternatively, this increase in BP may also be due to a transient increase in vasopressin release (3, 18).

As measured by telemetry, ICV infusion of Na⁺-rich aCSF only caused a transient (3 days) increase in HR. As measured by intra-arterial catheter, ICV infusion of Na⁺-rich aCSF tends to increase (the present study) or significantly increases (11) HR, even after 2 wk. Conscious rats are likely under more stress when a conventional catheter is used, and the HR response to stress is magnified by ICV infusion of Na⁺-rich aCSF. The return of resting HR to normal suggests that the sympathoexcitation by an increase in CSF [Na⁺⁺] (3, 15) is not associated with persistent cardiac sympathoexcitation.

Diurnal differences (night vs. daytime) in MAP and HR were about 5 mmHg and 35 beats/min during the control period. This diurnal variation in BP, but not HR, increased by 50% within 1 day of ICV infusion of Na⁺-rich aCSF. Aldosterone synthase inhibition did not affect the increase in resting BP and diurnal variation on the first day but subsequently blocked both. The diurnal variation in BP was not affected during ICV infusion of aCSF. These findings suggest that as a result of ICV infusion of Na⁺-rich aCSF locally produced aldosterone also contributes to the regulation of diurnal rhythms by the CNS. In Dahl S rats, high salt intake exaggerates the amplitude of circadian variations in BP (14, 22) and blunts the amplitude of the circadian expression of peripheral clock genes (22). Whether these changes also depend on aldosterone and MR in the CNS has not yet been studied.

Perspectives and Significance

The present study demonstrates that in Wistar rats a small increase in CSF [Na⁺⁺] appears to increase local synthesis of aldosterone and corticosterone in the hypothalamus. This aldosterone is the main agonist responsible for the stimulation of MR in the CNS and therefore the activation of central path-ways leading to sympathetic hyperactivity and hypertension. It remains to be determined by means of integrative and molecular approaches how an increase in CSF [Na⁺⁺] increases aldosterone synthesis in the brain, and whether in salt-sensitive animal models high salt intake also enhances local synthesis of aldosterone in the brain leading to sympathetic hyperactivity and hypertension.

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GRANTS

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DISCLOSURES

A. Y. Jeng is an employee of Novartis Institutes for BioMedical Research.

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