Maternal dehydration contributes to the development of salt sensitivity of blood pressure (SSBP) in offspring, with its influence likely tied to an elevation in vasopressin secretion.

Kim YB, PhD, Jung WW, PhD, Jin X, MD, PhD., Kang HK, MS, Kim YI, PhD.
Department of Physiology and Neuroscience Research Institute, Korea University College of Medicine, Seoul 02841, Republic of Korea

Abstract

This study investigated whether maternal dehydration programs SSBP and abnormal glucose metabolism (AGM) traits in offspring, both highly predictive of diverse cardiovascular conditions. Physiological studies were conducted with rat offspring, classified into two groups: those born to rat mothers with a 35% drinking water restriction during pregnancy and lactation (referred to as "experimental offspring"), and those born to mothers with unrestricted water access ("control offspring"). In the control group, a four-week salt challenge involving 8% NaCl-containing chow, initiated at seven weeks of age, did not significantly alter systolic blood pressure (SBP), regardless of sex. Conversely, the experimental group exhibited a marked SBP increase post-salt challenge, especially in males. Notably, glucose loading (200 mg/kg body weight) administered to both control and experimental offspring, exposed to a 32% sugar-containing drinking fluid regimen for 0-10 weeks, did not lead to abnormal blood sugar elevation. Further investigations unveiled that maternal water restriction's impact on the salt challenge-induced SBP response in male experimental offspring was counteracted by maternal conivaptan (non-selective vasopressin antagonist) treatment (22 ng/hour, sc.) during pregnancy. Additionally, these studies underscored a substantial rise in the percentage of vasopressin neurons displaying excitatory GABAergic postsynaptic potentials in the supraoptic nucleus of male experimental offspring post-salt challenge, a phenomenon absent in the control group. In summary, these findings suggest that maternal dehydration contributes to the development of SSBP trait in offspring. The programming and expression of this trait in male offspring appear linked to heightened vasopressin secretion, potentially regulated by excitatory GABAergic mechanisms.

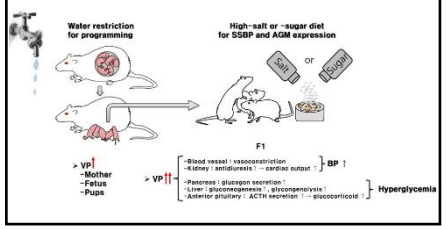
Introduction

SSBP and AGM are significant clinical indicators strongly linked to the emergence of hypertension and diabetes. A recent investigation conducted by our team unveiled that when pregnant or lactating mother rats excessively consume salt, their offspring (F1 generation) develop SSBP due to the excessive release of vasopressin (VP) (Kim et al., 2020, J. Mol. Cell. Cardiol. 150: 12-22). This discovery led to two noteworthy insights regarding this trait's manifestation. Firstly, the heightened VP secretion triggers SSBP by means of both vasoconstrictive and antidiuretic effects. Secondly, the pivotal factor driving augmented VP secretion lies in the transformation of inhibitory GABA signaling to an excitatory state in VP neurons.

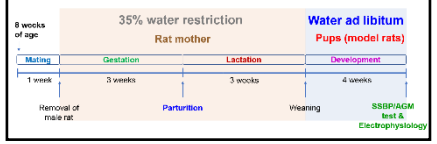
Beyond its role in vasoconstriction and antidiuresis, VP also contributes to elevated blood glucose levels by stimulating corticotropin secretion, hepatic glycogenolysis, gluconeogenesis, and pancreatic glucagon secretion (Melander, 2016, Ann Nutr Metab 68: 24-28). Consequently, the escalated VP secretion stemming from excessive salt consumption could potentially lead to hyperglycemia, possibly contributing to the development of AGM over time. However, this hypothesis has yet to receive empirical confirmation.

In the context of promoting VP secretion by raising plasma osmolality during pregnancy/lactation, both excessive salt intake and insufficient water intake are influential stimuli. In fact, the latter is more prevalent and is associated with detrimental eating behaviors/disorders in pregnant women that could negatively impact fetal well-being. In this study, we put forth the hypothesis that inadequate maternal water intake could program traits like SSBP and/or AGM in the offspring through mechanisms dependent on VP. Furthermore, we aimed to gather evidence supporting the notion that the shift from inhibitory to excitatory GABAergic transmission within VP neurons contributes to VP overproduction, thereby contributing to the manifestation of SSBP or AGM in adult offspring.

Proposed mechanisms for the developmental programming and expression of SSBP and AGM in the offspring of water-restricted rat dam during pregnancy and lactation.



Experimental modeling



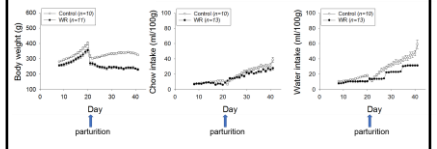
Test protocols

1) SSBP test: Salt challenge was given for 4 weeks by supplying the rat with 8% NaCl-containing chow as diet. This dietary challenge was instigated when the offspring reached the age of 7-8 weeks. SBP was measured before and during the salt challenge with a weekly interval using the tail-cuff method.

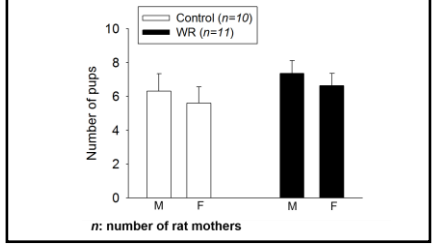
2) Oral glucose tolerance test (OGTT): Blood glucose levels were measured before and 30-120 min after glucose loading (200 mg/kg body weight) in Control and Experimental adult offspring that had been on 32% sugar-containing drinking fluid regime for 0-10 weeks. Drinking fluid and chow were removed for 8 hrs prior to the OGTT.

Results

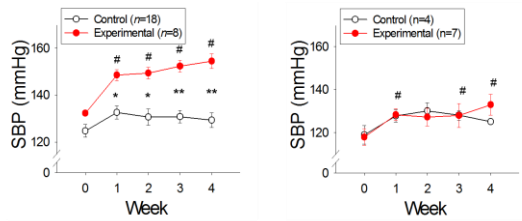
Body weight and the amounts of chow and water intake of control and water-restricted (WR) rat mothers before and after parturition



Numbers of pups born to control and WR rat mothers were not significantly different.

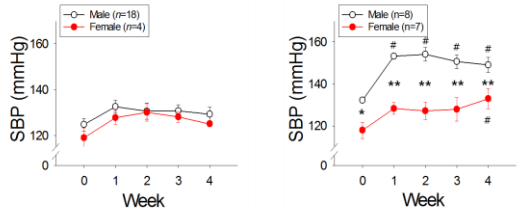


Effects of salt challenge on SBP in male (*left*) and female offspring (*right*)



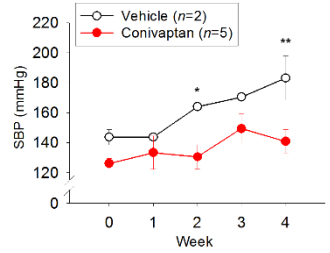
#: P<0.05 when compared to the value obtained at 0 week in the same group. *: P<0.05, **: P<0.001 when compared between control and experimental groups. *n*: number of rats. These rats were from different litters.

Effects of salt challenge on SBP in control (*left*) and experimental offspring (*right*)



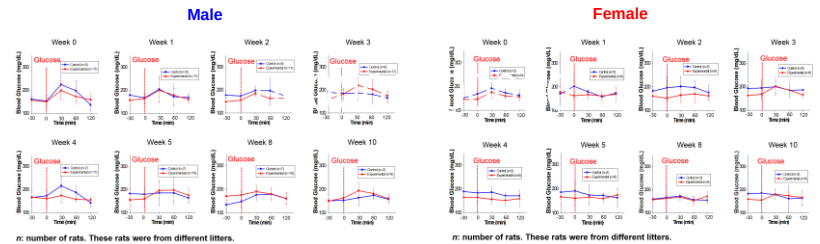
#: P<0.05 when compared to the value obtained at 0 week in the same group. *: P<0.05, **: P<0.001 when compared between male and female groups. *n*: number of rats. These rats were from different litters.

Maternal conivaptan treatment counteracted the maternal WR's impact on the salt challenge-induced SBP response in male offspring.



Conivaptan was treated throughout pregnancy at a rate of 22 ng/hour, with the use of osmotic mini-pump implanted subcutaneously in the scapular region. *: P<0.05, **: P<0.001 when compared between Vehicle and Conivaptan groups, *n*: number of rats. These rats were from different litters.

Lack of difference between control and experimental offspring in glucose tolerance



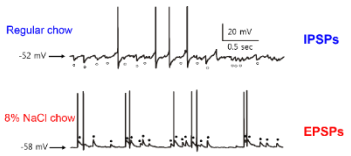
Electrophysiology

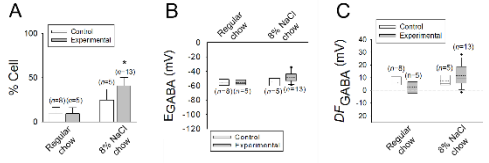
Slices of supraoptic nucleus (SON) were prepared from both control and experimental offspring, which had or had not been exposed to 8% NaCl-containing chow for 4 weeks. This dietary challenge was instigated when the offspring reached the age of 7-8 weeks.

Whole-cell recording were obtained from SON neurons; Micropipettes (tip diameter, 1.5–2.0 μm; 3–6 MOhm) pulled from borosilicate tubings (P-97; Sutter Instrument Co, Novato, CA) and filled with gramicidin (50 μg/mL)-containing solution (composition in mM: 143 K-gluconate, 2 KCl, 10 HEPES, and 0.5 EGTA; pH 7.2–7.3) were used for recording in a perforated configuration. To isolate GABAergic transmission from glutamatergic events, the NMDA blocker AP5 (100 μM) and the non-NMDA blocker DNQX (20 μM) were included in the slice-perfusing medium.

$GABA_A$ receptor-mediated PSPs, E_{GABA} and DF_{GABA} were analyzed.

Effect of salt challenge on $GABA_A$ receptor-mediated transmission in vasopressin neurons





These vasopressin neurons were recorded in the SON slices prepared from male experimental offspring, which had been on a regular or 8% NaCl-containing chow diet for 4 weeks.

(A) Percentage of neurons exhibiting $GABA_A$ receptor-mediated excitatory postsynaptic potentials (EPSPs). (B & C) E_{GABA} and DF_{GABA} values. *: P<0.05 within-group pairwise comparison with the data obtained under the "No salt challenge" condition (after Two-way ANOVA). *n*: number of litters. Electrophysiological data were from ≥3 cells for each litter. $DF_{GABA}=(E_{GABA}-$ resting membrane potential). All the data in this figure are from male offspring.

Conclusions

1) Maternal dehydration contributes to the development of SSBP trait in offspring, especially in males.

2) The programming and expression of this trait appear linked to increased vasopressin secretion.

3) Excitatory GABAergic mechanisms may underlie the heightened vasopressin secretion.