19 - RESPONSES OF BLOOD PRESSURE AND HEART RATE IN RATS SUBMITTED TO CHRONIC DEHYDRATION IN EARLY STAGES OF POST-NATAL

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INTRODUCTION

Changes of extracellular compartment osmolarity is felt by all the perfused tissues and may alter the volume metabolism and cell function (Strange, 1993). As a result of these cellular changes, sharp changes in osmolality can induce convulsions, paralysis, coma and, in extreme conditions, death (Bourque et al. 1994). Thus, precise regulation of the volume and osmolality of the extracellular compartment is critical for survival.

Behavioral adjustments consist in the regulation of sodium and water intake through changes in sodium appetite and thirst. Studies have shown that minimal elevations in plasma osmolarity or reductions in circulating blood volume (dehydration) are potent stimuli to develop the behavior of thirst. In mammals, a small increase in plasma osmolality 1-2% or 8-10% reduction in the volume of extracellular compartment are sufficient to induce water intake in these animals (Antunes-Rodrigues et al, 2004;. Fitzsimons 1998) .

Besides the seat, sodium appetite behavior is an important component for the maintenance of serum osmolarity. In mammals and some birds, decreases in plasma sodium concentration or the daily intake of salt are potent stimuli for which develops sodium appetite, and this inherent behavior of these species is necessary for homeostasis is maintained in the extracellular compartment (Fitzsimons 1998; BEAUCHAMP et al, 1990)..

The inefficiency of this set of adjustments can cause pathogens, from which we hypertension. Numerous experimental and epidemiological studies have suggested that diet soda is a major contributor to the development of hypertension (KEYS, 1970; HORAN, et al., 1985; LAW, et al, 1991;. Simons-Morton, Obarzanek, 1997).

Currently, studies suggest that the development of diseases in adulthood is related to specific conditions occurring in the early stages of life, including the prenatal phase (BARKER et al, 1989). Malaga et al., 2005 showed that mothers who experienced episodes of vomiting and dehydration during the first three months of pregnancy in adolescence produce children who had lower sensitivity to sodium and elevated systolic blood pressure. Thus, these authors showed that the sensitivity to sodium and blood pressure can be determined before birth through different maternal and fetal influences, including changes in hidromineral homeostasis.

As previously mentioned, several studies have shown that prenatal different influences such as maternal dehydration alter the sensitivity sodium appetite, which could favor the onset of hypertension. However, none of these studies bothered to assess whether changes during childhood could cause changes in these parameters in adulthood.

Thus, in rats induced by postnatal, analysis of induced water, sodium, blood pressure and heart rate period dehydration intake sought to determine whether the decrease in volume of the extracellular compartment in postnatal stages is able to generate changes in sodium appetite, and then due to changes become a risk factor for the development of hypertension.

METHODS

1. Animal model.

All experiments were performed on young Wistar rats, 5 and 21 days of age, provided by the Central Animal Laboratory of the Federal University of São Paulo, maintained with tap water ad libitum. The protocol that was conducted was approved by the Research Ethics Committee of this University under the number 0637-07.

2. Dehydration induced by administration of furosemide.

Dehydration in young animals was obtained by subcutaneous administration of furosemide (10 mg / kg body mass) into two groups: the first group received administration of furosemide from the fifth day of life (FURO - Day 5): the second group received administration of furosemide from the twenty-first day of life (FURO - day 21). As controls, two groups of animals received a subcutaneous dose of saline (0.9% NaCl). Three weekly administrations were performed up to two months.

3. Analysis of water intake and sodium.

Three weeks after the end of treatment (Administration of Furosemide and 0.15 Molar NaCl), adult animals of these groups were subjected to a test of intake-induced sodium and water. For both animals were individualized and treated with subcutaneous administration of furosemide (10 mg / kg body weight) and remain free access to water and food for twenty-four hours. Twenty-four hours after the administration of furosemide, a burette containing water and one containing saline (0.3 M NaCl) were offered to the animals and they had free access to solutions. The volume consumed was measured at 30 minute intervals for two hours. The animals underwent five to six intake induced tests for the analysis of water and sodium intake.

4. Registration of blood pressure (BP) and heart rate (HR).

For the recording of blood pressure and heart rate animals were anesthetized with sodium pentobarbital (40 mg / kg, iv) after induction with halothane (2% in 100% O2). The femoral artery and the right femoral vein were cannulated for recording blood pressure, heart rate (HR) and infusion of drugs, respectively. After tracheotomy was performed in order to reduce airway resistance.

The pulsatile arterial pressure (PAP) was obtained by connecting the arterial cannula to a pressure transducer coupled to an amplifier (ETH-2000 CB SCIENCES INC) and a system for acquiring and analyzing data (PowerLab, ADInstruments). Mean arterial pressure (MAP) was calculated from the signal of PAP and HR instantaneous signal frequency PAP was used.

5. Statistical Analysis.

The experimental data (changes in water and sodium intake, MAP and HR) are expressed as mean ± SEM (standard error of the mean) and analyzed using analysis of variance two-way repeated measures, followed by Newman-Keuls test , where it reaches the critical value of assuming $p < 0.05$.

RESULTS

Variation in Body Mass Produced For Furosemide Administration.

During the treatment with subcutaneous administration of furosemide (10 mg / kg) 3 times per week, examination of body weight showed a reduction of body mass in the experimental group (furosemide) compared with the control group (220 ± 4.3 * V 259 ± 3.3 grams).

Effect of Administration of Furosemide in Sodium and Water Intake in Rats Treated with Furosemide From The 5th and the 21st day of life.

The analysis of cumulative water intake (Figure 1A) and sodium (Figure 1B) in animals treated with furosemide (10 mg / kg) from the 5th day of life 2 hours after the start of the tests showed no difference in intake when compared with the control group. However, there is a difference between the two groups when compared with the baseline - Time 0. Similar results were obtained from animals subjected to dehydration from day 21 of life. As can be seen in Figure 2A and Figure 2B, both the cumulative water intake as sodium showed no difference in comparison with the control group, however, we observed a difference between the two groups when compared with the baseline - Time 0 .

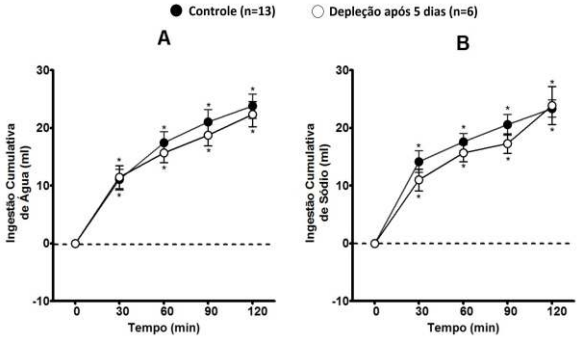


Figure 1. Mean ± SEM of the cumulative water intake (A) and sodium - 0.3 Molar (B) animals that underwent depletion of extracellular compartment by the administration of furosemide (10 mg / kg) from the 5th day of life. * Different from time 0 (p = 0.05)

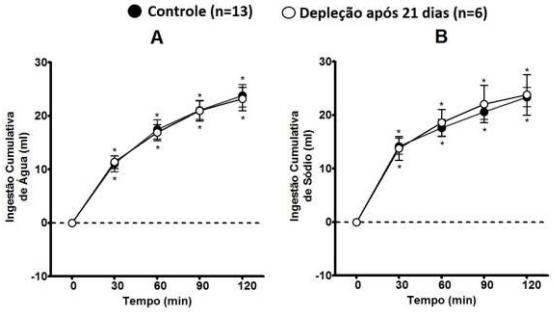


Figure 2. Mean ± SEM of the cumulative water intake (A) and Sodium - 0.3 Molar (B) animals that have undergone depletion of the extracellular compartment by the administration of furosemide (10 mg / kg) from day 21 of life. * Different from time 0 (p = 0.05)

Effect of Administration of Furosemide on Blood Pressure Values and Basal Heart Rate in Rats Treated From The 5th Day of Life.

The graphs in Figure 3 show the baseline blood pressure (MBP) and heart rate (HR) of the control group compared with the experimental group treated with furosemide. As can be seen at the end of the treatment period the basal levels of PAM are significantly higher (126 ± 2.9 mmHg vs 139.9 ± 3 mmHg) while the FC showed reduced basal values (411 ± 3.9 bpm vs 380 ± 4 bpm).

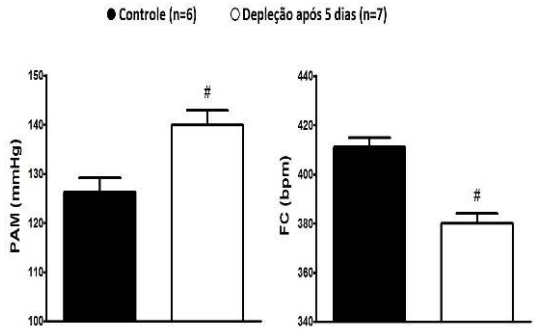


Figure 3. Mean ± SEM values for mean arterial pressure (MAP) and heart rate (HR) animals that underwent depletion of extracellular compartment by the administration of furosemide (10 mg / kg) from the 5th day of life. # Different from the time 0 (p = 0.05)

DISCUSSION

Previous studies have shown that the sensitivity to sodium and development of hypertension in adult stages can be determined before birth, through different maternal-fetal influences, including changes in hidromineral homeostasis. However, in these studies has not identified the possible role of postnatal stages in determining the sensitivity to sodium and consequent hypertension in adult stages. The results obtained in this study indicate that changes in fluid balance promoted in postnatal stages do not change-induced water and sodium intake. However these changes in postnatal stages were capable of promoting increased blood pressure in adult animals. These results indicate that postnatal stages are crucial for establishing the levels of blood pressure, and that changes in fluid balance in these phases are able to promote changes in the center responsible for the control of blood pressure, which results in increased pressure blood in adult animals.

Several studies have shown that maintenance of osmolality and plasma volume is essential for cellular homeostasis. Thus, changes in plasma sodium concentration or blood volume triggers a set of behavioral and vegetative adjustments that aim to correct these deviations, restoring physiological conditions. The inefficiency of this set of adjustments can cause pathogens, from which we hypertension. Experimental and epidemiological studies showed that the increase in sodium appetite contributes to the development of hypertension (Keys, 1970;. Horan et al, 1985, Law et al, 1991;. Simons-Morton; Obarzanek, 1997). Increases in blood pressure have been described in populations with high consumption of sodium in their diets (HORAN et al, 1985).

Recent studies suggest that the development of diseases in adulthood is related to specific conditions occurring in the early stages of life (BARKER et al, 1989). Bao et al. Demonstrated in 1995 that the risk of developing hypertension in adult life is related to blood pressure in the early stages of life. Corroborating this idea, Nicolaidis et al., 1990 showed that pregnant rats subjected to extracellular dehydration produce children with increased sodium appetite. These results differ from those obtained in our study, where the dehydration induced in postnatal stages did not change-induced water and sodium intake. Together, these results demonstrate that the organization of the neural substrate responsible for the intake of sodium and water occurs in prenatal stages, so only changes in fluid balance in uterine phases can jeopardize these behavioral adjustments.

Epidemiological studies show that mothers who experienced episodes of vomiting and dehydration during the first three months of pregnancy in adolescence produce children who had elevated systolic blood pressure (MALAGA et al., 2005). Our results corroborate and extend the findings of the MALAGA et al., 2005, since, in the early stages induced postnatal dehydration caused increased blood pressure in adult rats. These results show that not only uterine stages, but also the first post-uterine stages are critical to the determination of blood pressure in adult stages.

The results so far demonstrate that alterations in homeostasis hidromineral early post-uterine life do not seem to alter significantly the sodium appetite, but are fundamental for the determination of blood pressure. We believe that these results are highly relevant one made that hypertension is a disease that currently affects more human. However, it is noteworthy that the use of sodium thiopental anesthetic used for the recording of blood pressure and heart rate could mask the real value of blood pressure levels, since this anesthetic has a well-known sympathomimetic action.

Thus, a registry model in awake rats should be used to confirm the results obtained in this study.

CONCLUSIONS

In the present study demonstrated that changes in hidromineral homeostasis in rats during the postnatal period do not seem to change the sodium appetite, however seem to be crucial for determining baseline levels of blood pressure and heart rate.

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RESPONSES OF BLOOD PRESSURE AND HEART RATE IN RATS SUBMITTED TO CHRONIC DEHYDRATION IN EARLY STAGES OF POST-NATAL.

ABSTRACT

The purpose of this study was to determine whether the dehydration induced by furosemide in young rats alter the sensitivity to sodium appetite and blood pressure levels (BP) in adulthood. Young Wistar rats (5 and 21 days of life) were submitted to dehydration through furosemide subcutaneous injections (FUR) (10mg/ kg of body mass), control group received subcutaneous administration of saline (NaCl 0, 15M). Induction of dehydration occurred three times a week for five to seven weeks. After treatment period the animals had four weeks for recovery, moreover they were submitted to an induced intake test for water and sodium. During the test, animals were treated individually with injections of subcutaneous FUR. One day after FUR administration, we allowed free access to water and NaCl 0.3 Molar burettes offered in cages. Volume intake was measured during 30 minutes intervals for two hours. After the end of animals test, they were anesthetized with thiopental and prepared for mean arterial pressure (MAP) and heart rate (HR) recorder. We observed after dehydration, in 21 days rats, similar behaviors in both control (N = 13) and the furosemide. Similar results were obtained in animals treated with FUR from the 5th day of life. Furthermore, in FUR treated rats there was an increase in MAP and reduction in HR when compared to the control group. The results demonstrated changes in homeostasis fluid during early post-uterine life. There were no significant changes in sodium appetite. However, sodium appetite appears to be crucial for determining the levels of BP.

KEYWORDS: Sensitivity to Sodium; diuretic; Blood Pressure; Electrolyte control.

RÉPONSES DE LA PRESSION ARTÉRIELLE ET LA FRÉQUENCE CARDIAQUE RATS SOUMIS AU DÉSHYDRATATION CHRONIQUE DANS DES STADES PRÉCOCES DE LA POST-NATAL.

RÉSUMÉ

Des études antérieures ont montré que la sensibilité à la prise de sodium (SS) peut être déterminé avant la naissance. Cependant, aucune de ces études a évalué si les changements au début de la vie extra-utérine pourraient également promouvoir des changements dans cette sensibilité et la pression artérielle (PAM). Objectif: déterminer si induite par l'administration de furosémide (FUR) chez le rat pendant la période postnatale déshydratation altère la SS et de la PAM à l'âge adulte. Méthodes: 5 jeunes et 21 jours rats ont été soumis à la déshydratation par l'application sous-cutanée de la fourrure (10 mg / kg). Après la période de déshydratation, les animaux ont eu quatre semaines de récupération et on les soumet à un test de prise induite de l'eau et le sodium. Pour la petite histoire les animaux PAM ont été anesthésiés et une canule. Résultats: Nous avons constaté que, après induite par l'administration de la fourrure chez la souris 5 et 21 jours, à la fois le groupe témoin et le groupe de déshydratation FUR eu des comportements similaires en ce qui concerne la consommation d'eau et de sodium. En ce qui concerne les niveaux de PAM et la FC observé que, après un traitement avec de la fourrure chez les rats de la cinquième journée de la vie il y avait une augmentation dans les niveaux de base du PAM et de la réduction des ressources humaines par rapport au groupe de contrôle. Conclusion: Les résultats montrent que les changements dans l'homéostasie hidromineral chez les jeunes souris ne semblent pas modifier l'appétit de sodium, semble toutefois être crucial pour la détermination de la pression artérielle.

MOTS-CLÉS: Sensibilité à sodium; diurétique; Pression artérielle.

RESPUESTAS DE LA PRESIÓN ARTERIAL Y FRECUENCIA CARDIACA EN RATONES SOMETIDOS AL DESHIDRATACIÓN CRÓNICA EN PRIMERAS ETAPAS DE POST-NATAL.

RESUMEN

Estudios anteriores han demostrado que la sensibilidad a la ingesta de sodio (SS) se puede determinar antes del nacimiento. Sin embargo, ninguno de estos estudios evaluó si los cambios en el inicio de la vida extra-uterina también podrían promover cambios en esta sensibilidad y la presión arterial (PAM). Objetivo: Determinar si la inducida por la administración de furosemida (FUR) en ratas en el período postnatal deshidratación altera la SS y la PAM durante la edad adulta. Métodos: Los 5 jóvenes y 21 días ratas fueron sometidas a deshidratación por aplicación subcutánea de FUR (10 mg / kg). Después del período de deshidratación, los animales tuvieron cuatro semanas de recuperación y se sometieron a una prueba para la ingesta inducida de agua y sodio. Para el registro de los animales de PAM fueron anestesiados y canularon. Resultados: Se encontró que, después de inducida con la administración del FUR en ratones 5 y 21 días, tanto en el grupo control y el grupo de deshidratación FUR tenido comportamientos similares en cuanto a la ingesta de agua y sodio. En cuanto a los niveles de la PAM y FC observado que después del tratamiento con FUR en ratas desde el quinto día de vida se registró un aumento en los niveles basales de MAP y la reducción de recursos humanos en comparación con el grupo control. Conclusión: Los resultados demuestran que los cambios en la homeostasis Hidromineral en ratones jóvenes no parecen alterar el apetito de sodio, sin embargo parece ser crucial para la determinación de la presión arterial.

PALABRAS CLAVE: Sensibilidad al sodio; diurético; La presión arterial.

RESPOSTAS DA PRESSÃO ARTERIAL E FREQUENCIA CARDÍACA EM RATOS SUBMETIDOS À DESIDRATAÇÃO CRÔNICA EM FASES INICIAIS DO PERÍODO PÓS-NATAL.

RESUMO

Estudos anteriores têm demonstrado que a sensibilidade a ingestão de sódio (SS) pode ser determinada antes do nascimento. No entanto, nenhum desses estudos avaliou se alterações no início da vida extra-uterina poderiam também promover mudanças nesta sensibilidade e na pressão arterial (PAM). Objetivo: determinar se a desidratação induzida pela administração de furosemide (FUR) em em ratos no período pós-natal altera a SS e a PAM durante a fase adulta. Métodos: Ratos Wistar jovens de 5 e 21 dias foram submetidos à desidratação através da aplicação subcutânea de FUR (10mg/kg). Após o período de desidratação, os animais tiveram quatro semanas de recuperação e foram submetidos a um teste de ingestão induzida de água e sódio. Para o registro da PAM os animais foram anestesiados e canulados. Resultados: Verificamos que, após desidratação induzida com administração de FUR nos ratos com 5 e 21 dias de vida, tanto o grupo controle como o grupo FUR tiveram comportamentos semelhantes em relação à ingestão de água e de sódio. Em relação aos níveis de PAM e FC observamos que após o tratamento com FUR em ratos a partir do 5º dia de vida houve um aumento dos níveis basais de PAM e uma redução da FC quando comparado ao grupo controle. Conclusão: Os resultados obtidos demonstram que alterações na homeostase hidromineral em ratos jovens não parecem alterar o apetite ao sódio, entretanto parecem ser fundamentais para a determinação dos níveis de pressão arterial.

PALAVRAS-CHAVE: Sensibilidade a Sódio; Diurético; Pressão Arterial.