Sex differences in blood pressure response to continuous ang II infusion: Involvement of sex hormones and sex chromosome complement

Dadam, Florencia; Vivas, Laura; Caeiro, Ximena E.

Instituto de Investigación Médica M. y M. Ferreyra, INIMEC-CONICET-Universidad Nacional Córdoba. Córdoba, Argentina. E-mail: mariafdadam@gmail.com xcaeiro@immf.uncor.edu

Introduction: Cardiovascular diseases are the leading cause of death in men and women. The renin angiotensin system (RAS) plays a major role in the regulation of blood pressure (BP), however a growing body of evidence demonstrate that the pressor response to Ang II is sexually dimorphic under physiological and pathophysiological circumstances. But why do male and female show differences in RAS blood pressure modulation? Sex steroids can induce organizational (long-lasting or permanent) effect during critical periods of development but can also impart (temporary or reversible) activational effects. Furthermore, males and females also carry different sex chromosome complements (SCC:XY/XX) and thus are influenced throughout life by different genomes. Previous evidence demonstrate a modulatory effect of SCC in RAS receptors expression (at brain and renal levels), as well as in the Ang II sexually dimorphic bradycardic barroreflex and hypertensive responses.

Objective: To evaluate the different factors involved in the sexual diferences on changes in mean arterial pressure (MAP) in a 30 min Ang II infusion protocol.

Material and Methods: We use mice of the "four core genotype" model, in which the effect of gonadal sex and SCC is dissociated, allowing comparisons of sexually dimorphic traits between XX and XY females as well as in XX and XY males. Comparing these genotypes, it is possible to segregate the role of a) SCC (comparing mice with the same gonadal type but different SCC, XX vs. XY) b) sex (females vs male) and c) the interaction of SCC and sex factors. To evaluate the modulatory action of SCC and the organizational hormonal effects on a 30 min-Ang II infusion protocol, mice of the four genotypes were gonadectomized (GDX) and 15 days later their BP was measured under urethane anesthesia (control group – CON). We also analized, in a separate group of mice, the activational effect of estradiol on blood pressure response during Ang II

infusion; for hormonal replacement experiments GDX mice were daily injected with ß-estradiol (2ug/g) for a 4 day period (ß-estradiol group – E2).

Results: The statistical analysis indicated an interaction of SCC and organizational-sex factors {F(1.25)=7.93;p<0.01}; XX-male/GDX-CON, XY-female/GDX-CON and XX-female/GDX-CON mice showed an increase in MAP due to Ang II infusion, while no changes were observed in XY-males/GDX-CON mice. Furthermore, this increase in MAP was reversed by the activational effect of ß-estradiol (CON vs. E2 {F(1,59)=23,03 p<0,01 }) in XX-male/GDX-E2, XY-female/GDX- E2 and XX-female/GDX-E2, while no effect on blood pressure was observed in XY-male/GDX- E2.

Conclusion: In absence of the activational hormonal effects an interaction between the CCS and the organizational effects of the sex hormones differently modulate changes in the arterial pressure during Ang II infusion. Furthermore, estrogen replacement exerts an important activational effect by preventing the increase in blood pressure observed in most groups, except in XY-male/GDX.

Keywords: Renin angiotensin system, Sex chomosome complement, ß-estradiol, four core genotype s mouse model.

Supported: CONICET, FONCyT, CAEN, Roemmers Foundation.