Physiology & Behavior 152 (2015) 416–421

Contents lists available at ScienceDirect

Physiology & Behavior

journal homepage: www.elsevier.com/locate/phb

Review

Sex differences in body fluid homeostasis: Sex chromosome complement influences on bradycardic baroreflex response and sodium depletion induced neural activity

L. Vivas *, F.M. Dadam, X.E. Caeiro

Instituto de Investigación Médica Mercedes y Martín Ferreyra, INIMEC, CONICET, Universidad Nacional de Córdoba, Córdoba, Argentina

HIGHLIGHTS

- Sex chromosome complement influences on angiotensin-induced responses
- XX-sex chromosomes induce a facilitated baroreflex response to angiotensin II.
- Sexually dimorphic sodium appetite is in part a result of gonadal steroid action.
- XX-sex chromosomes' effect on sodium depletion-induced neural activity at SFO and AP

ARTICLE INFO

Article history:
Received 28 February 2015
Received in revised form 3 August 2015
Accepted 4 August 2015
Available online 8 August 2015

Keywords:
Sexual dimorphism
Sex chromosome complement
Sodium appetite
Angiotensin II
Subfornical organ
Area postrema
Baroreflex response
FOS-ir

ABSTRACT

Clinical and basic findings indicate that angiotensin II (ANG II) differentially modulates hydroelectrolyte and cardiovascular responses in male and female. But are only the activational and organizational hormonal effects to blame for such differences? Males and females not only differ in their sex (males are born with testes and females with ovaries) but also carry different sex chromosome complements and are thus influenced throughout life by different genomes. In this review, we discuss our recent studies in order to evaluate whether sex chromosome complement is in part responsible for gender differences previously observed in ANG II bradycardic-baroreflex response and sodium depletion-induced sodium appetite and neural activity. To test the hypothesis that XX or XY contributes to the dimorphic ANG II bradycardic-baroreflex response, we used the four core genotype mouse model, in which the effects of gonadal sex (testes or ovaries) and sex chromosome complement (XX or XY) are dissociated. The results indicate that ANG II bradycardic-baroreflex sexual dimorphic response may be ascribed to differences in sex chromosomes, indicating an XX-sex chromosome complement facilitatory bradycardic-baroreflex control of heart rate. Furthermore, we evaluated whether genetic differences within the sex chromosome complement may differentially modulate the known sexually dimorphic sodium appetite as well as basal or induced brain activity due to physiological stimulation of the renin–angiotensin system by furosemide and low-sodium treatment. Our studies demonstrate an organizational hormonal effect on sexually dimorphic induced sodium intake in mice, while at the brain level (subfornical organ and area postrema) we showed a sex chromosome complement effect in sodium-depleted mice, suggesting a sex chromosome gene participation in the modulation of neural pathways underlying regulatory response to renin–angiotensin stimulation.

Contents

* Corresponding author at: Friuli 2434, 5016 Córdoba, Argentina.
E-mail address: lvivas@immf.uncor.edu (L. Vivas).

http://dx.doi.org/10.1016/j.physbeh.2015.08.010
0031-9384/

Differences between the sexes have been recognized at biochemical, cellular, and physiological levels, but historically most epidemiological and basic studies have been performed in male subjects, assuming that males and females are similar, differing only in the magnitude of the response. However, the principles learned in male models do not necessarily apply to females.

There is significant data indicating the participation of the activational and organizational effects of gonadal steroids in sexual dimorphism [1,2]; however, are gonadal steroids the only ones to blame for such differences? Although the role of gonadal steroids in sexual dimorphism is undeniable, a growing body of evidence indicates that some sexually dimorphic traits cannot be explained solely as a result of gonadal steroid action. Males and females differ not only in their sex (males are born with testes and females with ovaries) but they also carry different sex chromosome complements and are thus influenced throughout life by different genomes. In this way, genetic and/or hormone pathways may act independently or interact (synergistically/antagonistically) to modulate sexual dimorphic development [3,4,5,6].

Angiotensin II (ANG II) in the central nervous system differentially modulates hydroelectrolyte and cardiovascular parameters in males and females [7,8]. Furthermore, a growing number of studies have shown that dysfunction of the brain renin–angiotensin system (RAS) is implicated in the development of hypertension, and that males and females do not respond equally to hypertensive treatment with RAS inhibitors, reflecting a sexually dimorphic cardiovascular response to angiotensin [7]. For example, clinical and basic findings indicate a sexually dimorphic baroreflex control of heart rate (HR). The acute administration of ANG II in normotensive male and female patients induces increases in blood pressure of similar magnitude; however, in men, the bradycardic baroreflex response is blunted relative to that observed in women [9]. Likewise, studies carried out by Pamidimukkala et al. [10] have shown that, in male mice, the slope of ANG II-induced baroreflex bradycardia is significantly less than that evoked by phenylephrine, whereas female mice show the same bradycardic response to ANG II and phenylephrine [10].

Although clinical and experimental studies have addressed the activational modulatory effect of gonadal steroids on the baroreflex control of HR [10,11], classic hormonal manipulations have failed to cause sex reversal of the differences observed in ANG II-bradycardic baroreflex response. Thus, one of the aims of our studies was to test the hypothesis that sex chromosome complement (XX or XY) contribute to ANG II baroreflex sexual dimorphism, modulating the bradycardic baroreflex response. To this end, we used the four core genotype mouse model, in which the effect of gonadal sex (testes or ovaries) and sex chromosome complement (XX or XY) is dissociated. To remove any activational effect of sex hormones that might mask effects of sex chromosomes, adult conscious gonadectomized (GDX) mice were used. Comparing gonadal males and females after gonadectomy can test whether having testes or ovaries causes long-lasting differences in the phenotype (organizational effect) while comparing mice with the same gonadal type but with different sex chromosome complement (XX versus XY) makes it possible to determine whether genes residing in the sex chromosome complement differentially influence sexually dimorphic traits (Fig. 1).

As shown in Fig. 2, ANG II acute infusion produced, irrespective of gonadal sex, a different baroreflex response depending on the genetic sex (significant effect of sex chromosome complement factor). Both male and female mice with XX-sex chromosomes showed a facilitated baroreflex response when compared with GDX-XY male and female mice ($P < 0.005$). A 30 mm Hg increase in blood pressure in GDX-XX mice was accompanied by a decrease in HR of -163.19 ± 11.92 beats·min^{-1}, whereas in GDX-XY mice this response was attenuated (-76.82 ± 18.31 beats·min^{-1}). Thus, these data may indicate that the sexually dimorphic ANG II bradycardic baroreflex response may be ascribed to differences in sex chromosomes, indicating an XX-sex chromosome complement facilitatory bradycardic baroreflex control of HR [12].

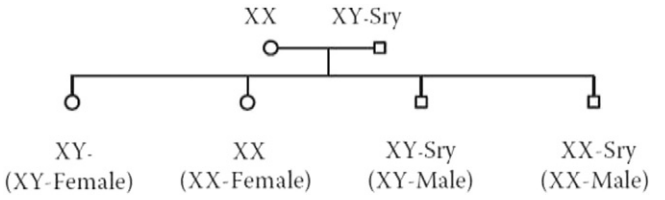

Fig. 1. Schematic representation of four core genotype mouse model. This mouse model combines a deletion of the testis-determining gene *Sry* from the Y chromosome (Y_) with the subsequent insertion of an *Sry* transgene onto an autosome. The *Sry* gene deletion in male mice (XY_) yields a female phenotype (ovaries). When the *Sry* transgene is inserted into an autosome of these mice, they have testes and are fully fertile (XY_*Sry*). The Y_ chromosome and the *Sry* transgene segregate independently; thus, four types of offspring are produced by breeding XY_*Sry* males to XX females: XX and XY_females (without *Sry* on the Y chromosome) and XX*Sry* and XY_*Sry* male mice (both with *Sry* in an autosome). All of the individuals possessing the *Sry* transgene develop testes and have a male external phenotype, regardless of their sex chromosome complement, whereas individuals lacking the transgene have ovaries and external female secondary sex characteristics. "Male" and "female" are defined here according to the gonadal phenotype: we refer throughout to XX and XY_ as XX and XY females and to XX*Sry* and XY_*Sry* as XX and XY male mice, respectively.

In this animal model we also evaluated the effect of another pressor agent (phenylephrine) on the baroreflex function in comparison with AngII response. As it has been previously demonstrated for males the reflex inhibition of HR in response to ANG II in GDX-XY male mice induced a blunted bradycardic response when compared with the phenylephrine response, while in GDX-XX females showed the same bradycardic baroreflex response to both phenylephrine and ANG II (Fig. 3). The analysis of the bradycardic baroreflex response in mice with XX-sex chromosome complement but with different gonadal sex (GDX-XX male and GDX-XX female mice) showed the same bradycardic baroreflex response to both pressor agents.

Furthermore, the comparison of female mice with different sex chromosome complements (GDX-XX female versus GDX-XY female) showed that the administration of phenylephrine in GDX-XY females resulted in a significantly lower baroreflex response when compared with the other genotypes. Although changes in blood pressure were

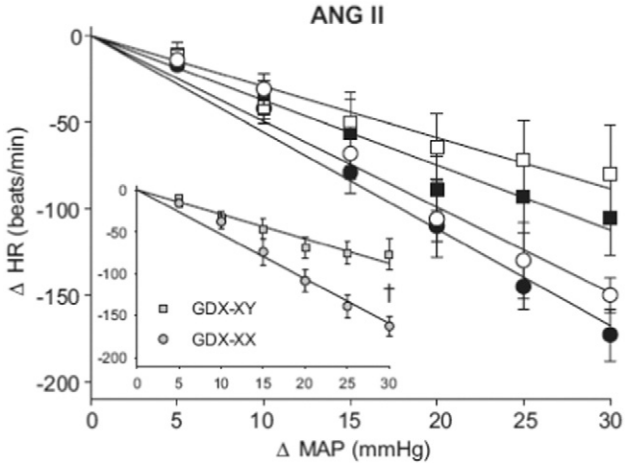

Fig. 2. Reflex bradycardic responses to angiotensin II (ANG II) infusion in MF1 gonadectomized (GDX) mice of the four core genotype. Graph shows mean relationship lines relating peak changes in heart rate (HR; delta HR) to increases in mean blood pressure (MAP; delta MAP) induced by Ang II. Black symbols and white symbols represent male and female mice respectively. Inset represents Ang II reflex bradycardic response in GDX-XY and GDX-XX mice, irrespective of gonadal sex. †$P < 0.05$, significant bradycardic baroreflex differences between GDX-XX and GDX-XY mice independent of gonadal sex; GDX-XY male (n = 6), GDX-XX male (n = 6), GDX-XY female (n = 6), and GDX-XX female (n = 5) mice.
(Reprinted with permission from Caeiro, X.E. et al., Hypertension, 58, 505–511, 2011.)