Slov Vet Res 2010; 47 (4): 155-8
UDC 57.08:591.46:612.4:599.323.4

Review Article

BEHAVIORAL CHARACTERIZATION OF STEROIDOGENIC FACTOR-1 KNOCKOUT MICE

Neža Grgurevič[1*], Stuart A. Tobet[2], Gregor Majdič[1,3]

[1]Center for Animal Genomics, Veterinary faculty, University of Ljubljana, Gerbičeva 60, 1000 Ljubljana, Slovenia; [2]College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, CO, 80523-1680, USA; [3]Institute of Physiology, Medical School, University of Maribor, Slomškov trg 15, 2000 Maribor, Slovenia

*Corresponding author, E-mail: neza.grgurevic@gmail.com

Summary: Sex differences in the brain are mainly caused by sex steroid hormones. Steroidogenic factor-1 is a key regulator of gonadal and adrenal development, and SF-1 knockout mice (SF-1KO) are born without gonads and adrenal glands and the region of the ventromedial nucleus of the hypothalamus (VMH) is reorganized. Due to the absence of gonadal hormones during embryonic development and alterations of the VMH, SF-1 KO mice provide an important model to study VMH dependent and hormonally independent sex differences in brain and behaviour. Initial studies did not show significant sex differences that could be attributed to sex chromosome effects, but provided interesting differences in aggressive and affiliative behaviours between genotypes, that may be attributable to the disrupted cellular organization of the VMH in SF-1 KO mice. However, further more focused behavioural studies also revealed some sex differences that could be also attributed to the action of sex chromosomes.

Key words: brain; sex differences; mouse; behaviour

Introduction

Differences in the brains between males and females have been observed in many levels of structure and function (1). One of the central questions is how and when these differences arise? Mammalian sexual differentiation begins with an expression of the *Sry* gene normally found on the Y chromosome and differentiation of the male gonads. After testes develop, circulating testosterone (T) leads to long-lasting changes in the structure of the male brain. It is now generally accepted that in rodents, the process of masculinization and defeminization is mediated by estradiol, derived from the local aromatization of T. In females, ovaries do not secrete significant levels of steroid hormones during prenatal development and many female brain characteristics develop in the absence of hormonal secretion (2). However, some studies suggest that development of female brain also requires active feminization and this process could be regulated by estradiol secreted from the ovaries between birth and puberty (3). Later in life, gonadal secretion of steroid hormones continues to induce less permanent sex differences via activational effects. These differences are sex-specific caused by ovarian and testicular secretions and could be eliminated by gonadectomy (2). In the last 10-15 years, a growing number of studies have shown that some sex differences in the brain could arise independently of gonadal hormones and putatively by different effects of genes, especially located on the X or Y chromosomes (4). Such sex differences, in mice, have been described in parental and aggressive behaviour (5), learning of habits (6), and sniffing and grooming of an intruder (7). In most behavioural studies it is difficult to distinguish between organizational and activational effects since gonadally intact mice are used (4). Therefore we used a novel model, agonadal mice with disruption of the gene coding for steroidogenic factor-1. Steroidogenic factor 1 (SF-1), officially designated NR5A, was initially discovered as a regulator of the cytochrome P450 steroidogenic enzymes (8). Subsequent studies

Received: 13 September 2010
Accepted for publication: 15 November 2010

have defined broader roles for SF-1 in development and function of the hypothalamus-pituitary-gonadal axis. SF-1 KO mice are born without gonads and adrenal glands and have male to female sex reversal of secondary sex structures. The organization of the region that would normally contain the ventromedial nucleus of the hypothalamus (VMH) and gene expression in pituitary gonadotropes is also markedly altered in SF-1 KO mice (9). After neonatal corticosteroid injections and adrenal transplantation these mice can be studied in adulthood (10). Due to lack of gonadal hormones during embryonic development and alterations of the VMH SF-1 KO mice provide an important tool for delineating the roles of gonadal hormones and the VMH in a variety of sex dependent aspects of physiology and behaviour.

Behavioural analyses of SF-1 knockout mice

In a recent study SF-1 KO (genetically females and males) and WT mice were gonadectomized prior to puberty and tested for social behaviours. In these studies, no sex differences were found between chromosomally male and female (XX and XY) SF-1 KO mice in three different hormonal settings – in hormonally naïve mice and in mice primed with either testosterone or estradiol and progesterone. Nevertheless, these studies provided interesting results with regard to aggression in both hormonally naïve and testosterone treated SF-1 KO mice. Hormonally naïve SF-1 KO mice, in particular females, were aggressive against intruder mice (11). However, this aggression was moderate aggression and could be possibly attributed to increased anxiety like behaviour in SF-1 KO mice that was also found in other testing paradigms (e.g., EPM, (12)) and another study using VMH specific SF-1 knockout mice model (13). Interestingly, testosterone treatment reduced the aggression shown by SF-1 KO mice and induced strong aggressive behaviour only in WT male mice (11). This confirmed that testosterone during a developmental period is needed to display proper intermale aggressive behaviour as reported previously (14). Aromatization of T could be the major factor responsible for development of adult intermale aggression since ERαKO mice rarely display aggressive behaviour against bulbectomized males (15). In contrast, ERβKO (16) and testicularly feminized mice (17) do show normal intermale aggression.

In contrast to data for rats (18), our studies have shown that neonatal hormonal exposure is not necessary for proper expression of sex related behaviors in mice since both testosterone and estradiol/progesterone primed SF-1 KO mice display both male and female sex behaviour, respectively. Although lordosis quality was not scored in our initial studies with EB+P primed mice, we can speculate from the copulatory behaviour of male mice that SF-1 KO mice were less receptive than WT females and also that females were more receptive than males regardless of their genotype, and this was further confirmed in follow up studies (19). Lower receptivity of SF-1 KO mice could be due to the absence of gonadal hormones during development (3), or just as likely due to the altered organization of the VMH. It is well known that the VMH plays important role(s) in lordosis behaviour and, consistent with our findings, impaired lordosis was also found in CNS-specific SF-1 KO mice (20). So far it is not known if genetic factors contribute to defeminization of female sexual behaviour in males independently or in concert with gonadal hormones. Defeminization could be regulated through ERβ, since higher lordosis quotient was observed in ERβKO males compared to the WT males (21). It would be interesting to establish whether SF-1 KO males are partially defeminized and if this process is regulated through different Y linked genes, ERβ, or dopaminergic systems since expression of tyrosine hydroxylase is regulated by the *Sry* gene in the midbrain (22). Further experiments will be needed to test these hypotheses.

Acknowledgements

This work was supported by NIH grant MH61376 (S.A.T. and G.M.), ICGEB grant CRP SLO 06/02, ARRS (Slovenian research agency) grants P4-0053 and J7-2093 (G.M.).

References

1. Cooke B, Hegstrom CD, Villeneuve LS, et al. Sexual differentiation of the vertebrate brain: principles and mechanisms. Front Neuroendocrinol 1998; 19(4): 323–62.

2. MacLusky NJ, Naftolin F. Sexual differentiation of the central nervous system. Science 1981; 211(4488): 1294–302.

3. Bakker J, Baum MJ. Role for estradiol in female-typical brain and behavioral sexual differentiation. Front Neuroendocrinol 2008; 29(1): 1–16.

4. Arnold AP. Mouse models for evaluating sex chromosome effects that cause sex differences in non-gonadal tissues. J Neuroendocrinol 2009; 21(4): 377–86.

5. Gatewood JD, Wills A, Shetty S, et al. Sex chromosome complement and gonadal sex influence aggressive and parental behaviors in mice. J Neurosci 2006; 26(8): 2335–42.

6. Quinn JJ, Hitchcott PK, Umeda EA, et al. Sex chromosome complement regulates habit formation. Nat Neurosci 2007; 10(11): 1398–400.

7. McPhie-Lalmansingh AA, Tejada LD, Weaver JL, et al. Sex chromosome complement affects social interactions in mice. Horm Behav 2008; 54(4): 565–70.

8. Lala DS, Rice DA, Parker KL. Steroidogenic factor I, a key regulator of steroidogenic enzyme expression, is the mouse homolog of fushi tarazu-factor I. Mol Endocrinol 1992; 6(8): 1249–58.

9. Parker KL, Schimmer BP. Steroidogenic factor 1: a key determinant of endocrine development and function. Endocr Rev 1997; 18(3): 361–77.

10. Majdic G, Young M, Gomez-Sanchez E, et al. Knockout mice lacking steroidogenic factor 1 are a novel genetic model of hypothalamic obesity. Endocrinology 2002; 143(2): 607–14.

11. Grgurevic N, Budefeld T, Rissman E F, et al. Aggressive behaviors in adult SF-1 knockout mice that are not exposed to gonadal steroids during development. Behav Neurosci 2008; 122(4): 876–84.

12. Grgurevic N, Tobet SA, Rissman EF, Majdic G. SF-1 knockout mice – a novel model for behavioral studies from perspective of sex steroids and VMH structure. In: Society for behavioral neuroendocrinology annual meeting. Pacific Grove, USA, 2007.

13. Zhao L, Kim K W, Ikeda Y, et al. Central nervous system-specific knockout of steroidogenic factor 1 results in increased anxiety-like behavior. Mol Endocrinol 2008; 22(6): 1403–15.

14. vom Saal F S. Prenatal exposure to androgen influences morphology and aggressive behavior of male and female mice. Horm Behav 1979; 12(1): 1–11.

15. Ogawa S, Lubahn D B, Korach K S, et al. Behavioral effects of estrogen receptor gene disruption in male mice. Proc Natl Acad Sci U S A 1997; 94(4): 1476–81.

16. Ogawa S, Chan J, Chester A E, et al. Survival of reproductive behaviors in estrogen receptor beta gene-deficient (betaERKO) male and female mice. Proc Natl Acad Sci U S A 1999; 96(22): 12887–92.

17. Scordalakes E M, Rissman E F. Aggression and arginine vasopressin immunoreactivity regulation by androgen receptor and estrogen receptor alpha. Genes Brain Behav 2004; 3(1): 20–6.

18. Bonthuis P J, Cox K H, Searcy B T, et al. Of mice and rats: key species variations in the sexual differentiation of brain and behavior. Front Neuroendocrinol 2010; 31(3): 341–58.

19. Grgurevic N, Rissman EF, Tobet SA, Majdic G. Differentiation of sexual behavior potential in agonadal steroidogenic factor 1 knockout mice. In: Society for behavioral neuroendocrinology annual meeting. Groeningen, Netherlands, 2008.

20. Kim K W, Li S, Zhao H, et al. CNS-specific ablation of steroidogenic factor 1 results in impaired female reproductive function. Mol Endocrinol 2010; 24(6): 1240–50.

21. Kudwa AE, Michopoulos V, Gatewood JD, et al. Roles of estrogen receptors alpha and beta in differentiation of mouse sexual behavior. Neuroscience 2006; 138(3): 921-8.

22. Dewing P, Chiang CW, Sinchak K, et al. Direct regulation of adult brain function by the male-specific factor SRY. Curr Biol 2006; 16(4): 415–20.

PROUČEVANJE OBNAŠANJA MIŠI BREZ GENA SF-1

N. Grgurevič, S.A. Tobet, G. Majdič

Povzetek: Spolne razlike v možganih nastanejo predvsem zaradi delovanja spolnih hormonov. Steroidogeni faktor 1 (SF-1) je dejavnik, ki uravnava razvoj spolnih žlez in nadledvične žleze. Miši brez gena SF-1 (angl. Knockout; SF-1 KO) se rodijo brez spolnih in nadledvičnih žlez in imajo spremenjeno strukturo ventromedialnega jedra hipotalamusa (VMH). Zaradi pomanjkanja spolnih hormonov med embrionalnim življenjem in zaradi spremenjenega jedra VMH predstavljajo miši SF-1 KO pomemben model za proučevanje hormonsko neodvisnih in od VMH odvisnih spolnih razlik v možganih in v obnašanju. Naše začetne raziskave niso pokazale spolnih razlik, ki bi jih lahko pripisali vplivu spolnih kromosomov, vendar pa so pokazale zanimive razlike v agresivnem in socialnem obnašanju med kontrolnimi mišmi in mišmi brez gena SF-1, ki bi jih lahko pripisali spremenjeni strukturi jedra VMH. Pri bolj usmerjenih raziskavah v določene tipe obnašanja pa smo ugotovili nekatere zanimive razlike med spoloma tudi pri miših brez gena SF-1, ki kažejo na vpliv spolnih kromosomov na spolno različen razvoj možganov.

Ključne besede: možgani; spolne razlike;miš; obnašanje