The Male Prevalence in Autism Spectrum Disorders: Hypotheses on its Neurobiological Basis

Flavio Keller and Liliana Ruta

Introduction

Autism and the related disorders Pervasive Developmental Disorder Not Otherwise Specified (PDD NOS) and Asperger syndrome (AS) are neurodevelopmental conditions with strong heritability (Muhle et al., 2004) characterized by impairment in social-communicative skills and a restricted and repetitive pattern of interests and behaviours. Together they are broadly referred to as autism spectrum disorders (ASD) (APA, 2000).

The widely accepted concept of a "spectrum" properly emphasizes the variability in the phenotypic characteristics within this condition (Volkmar et al., 2005) and opens a relevant debate on how to consider the clinical heterogeneity of the autistic core symptoms in terms of social impairment, communication deficit and restricted/repetitive behaviour.

The main two theories that addressed this issue are referred to as the "subgroup model" and the "severity model".

According to the subgroup model this variation might be explained in terms of discrete phenotypes within the disorder with unique, even if partially overlapping, gene contributions to the different aspects of the phenotype such as social interaction, language and interests (Silverman et al., 2002; Ronald et al., 2006; Shao et al., 2003).

On the other hand, the severity model assigns the different presentation of the core symptoms observed in autism to a continuous severity gradient with an additive genetic effect in terms of susceptibility – i.e. the more susceptibility genes a person has, the more severe the phenotype will be (Spiker et al., 2002; Constantino et al., 2004; Ring et al., 2008).

Unfortunately, although several twin and family studies (Bolton et al., 1994; Bailey et al., 1995) and linkage analyses (Veenstra-VanderWeele and Cook, 2004) have confirmed the roles of a number of possible candidate genes, and the two

F. Keller (✉)
Laboratory of Developmental Neuroscience, University Campus Bio-Medico, 00128, Roma, Italy
e-mail: f.keller@unicampus.it

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different approaches mentioned above – the subgroup model and the severity model – seem both very promising, a clear etiological cause for ASD has not yet been demonstrated. Some researchers hypothesize that other neurobiological processes in addition to genetic processes, occurring at critical sensitive periods for brain development, might exert a pathogenic role. Indeed, the continuous gradient hypothesis fits well with a disease model where epigenetic factors – either stemming from the environment or originating from within the organism itself – could modulate a basic genetic vulnerability for autism, leading to a continuum of severity of symptoms. This view is consistent with the increasingly recognized role of epigenetic modulation ("plasticity") of the genome, resulting in steady modifications of phenotypes (Zhao et al., 2007) and with the so-called "triple helix model" of organism development (Lewontin, 2000), according to which the outcome of development depends on three different but interacting players: genetic mechanisms, the context of the organism and the environment.

Neuroanatomical and Neurofunctional Features of Autism Spectrum Disorders in Relationship to Brain Sexual Dimorphisms

At present, data on neuroanatomical alterations in ASD are still too scanty and not sufficiently robust to be convincingly linked to specific neurofunctional features in ASD. Brain regions showing more robust neuroanatomical alterations, in vivo or post-mortem, include the temporal cortex, the hippocampus, the amygdala and the cerebellum (reviewed in Courchesne et al., 2005; Keller and Persico, 2003; Palmen et al, 2004; Schumann and Amaral, 2006).

The amygdala and the hippocampal formation show sexually dimorphic patterns of development in humans, with amygdala volumes increasing significantly more in males than in females and hippocampal volume increasing more in females (Giedd et al., 1997). Observations in rodents are partially consistent with these human findings. The amygdala has been found to be significantly larger in male mice (Koshibu et al., 2004). In the hippocampus two interesting effects have been described: (1) the dentate gyrus of the hippocampus has been found to be larger in male rats (Roof, 1993) and also in some mouse strains but not in others (Tabibnia et al., 1999); (2) a lateralization of the volume of the dentate gyrus has been found, with the volume of the right dentate gyrus being larger than the left, this effect being observed in both sexes. Interestingly, testosterone has been implicated in both effects. Observations in mice are also consistent with a peculiar sensitivity of the hippocampus and amygdala to sex hormones, since these two structures have been found to be disproportionately larger in adult compared to peripubertal mice (Koshibu et al., 2004).

The existence of sexual dimorphisms in temporal cortex and cerebellum has not been sufficiently investigated to date, as the bulk of animal model research has focused on regions most directly related to reproductive behaviours. However,

recent work suggests the existence of robust sex differences in the expression of oestrogen receptor (ER) α, ERβ and the ER G-protein-coupled receptor 30 (GPR30) in the cerebellum and amygdala of newborn hamsters (Canonaco et al., 2008). It will be very important to confirm these observations as well as extend them to the human brain.

Theories Accounting for the Male Prevalence of ASD

The existence of a sex bias in ASD, with a male to female sex ratio of 3–4:1 for autism (Lord and Schopler, 1987) and 8–9:1 for AS (Wing, 1981), as well as some characteristics of cognitive functioning and emotion perception in this condition have led some researchers to link autism to "maleness". A very intriguing theory developed by Baron-Cohen et al. considers autism as an "extreme form of male brain" (Baron-Cohen and Hammer, 1997; Baron-Cohen, 2002, 2003). According to the *Extreme Male Brain (EMB) Theory*, in fact, autistic individuals show an extreme pattern of the typical male brain functions.

This theory moves its steps from the good deal of evidence for a sexual dimorphism both in neuropsychological features (Kimura, 1999) and in brain neurobiology (Kimura, 1999; Allen et al., 1989; Aboitiz et al., 1992).

Indeed women are reported to be better, on average, at verbal and social tasks, showing stronger ability in "empathy", while men, as a group, are superior at "systemizing", targeting and visuo-spatial tasks.

At such tests as the "Empathy Quotient" (EQ), "Reading the Mind in the Eyes" or "Facial Expressions", females score higher than males but autistic individuals score even lower than unaffected males (Baron-Cohen et al., 2001; Baron-Cohen and Wheelwright, 2004). On the other hand, an opposite personality profile has been shown for the "Systemizing Quotient" (SQ) with males scoring higher than females and people with ASD scoring highest of all (Baron-Cohen et al., 2003). The same pattern of results has been obtained on the "Embedded Figures" Task and "Mental Rotation" Task (Baron-Cohen, 1998; Jolliffe and Baron-Cohen, 1997; Ring et al., 1999).

Sex differences have also been found in the pattern of cerebral lateralization, with some studies reporting women to be less lateralized for some cognitive functions and language, as displayed, for example, by a more symmetric pattern at the dichotic listening test (McGlone, 1980; Hiscock et al., 1993). However, controversy exists as other studies have not replicated these findings or have found left-handedness to be more common in males (Sommer et al., 2008).

Hemispheric Lateralization, Brain Sexual Dimorphisms and Foetal Testosterone

Sex hormones exert important organizing effects, determining both the anatomical and the functional asymmetry of the brain, present from birth or arising during

childhood with different developmental trajectories (Giedd et al., 1996). Consistent with this view, an important study by Goldstein et al. (2001), carried out on normal adult brains, has reported greater sexual dimorphisms in the brain volume of those regions that express high levels of androgen and oestrogen receptors during foetal development.

Indeed it has been presumed that sexual differentiation of the nervous system is primarily established perinatally and then actively maintained throughout life. Furthermore, evidence has been provided in rats that the pubertal hormone surge contributes to the post-natal preservation of sexual dimorphisms through sex-specific modulation of new cell addition to sexually dimorphic brain regions (the anteroventral periventricular nucleus of the hypothalamus, the sexually dimorphic nucleus of the preoptic area, and the medial amygdala). For each region, the sex that gains more cells during puberty has a larger volume in adulthood. Removing gonadal hormones before puberty eliminated these sex differences, indicating that gonadal steroids direct the addition of new cells during puberty to maintain and enhance sexual dimorphisms in the adult brain (Ahmed et al., 2008).

Brain sexual dimorphisms as well as sex differences in the hemispheric lateralization represent interesting target areas to be linked with the core symptoms of ASD.

While both phenomena may be related, it is important to distinguish between hemispheric lateralization and brain sexual dimorphism Tabibnia et al. (1999) suggested that androgen receptors may play a role in development of laterality in the dentate gyrus of the hippocampus, independently of any sexual dimorphism in this structure. In their study, they examined mice with a defective structural gene for androgen receptors (testicular feminization mutant or tfm mice) on a C57/BL6J background and found that the right granule cell layer volume in the dentate gyrus of the hippocampus was greater than the left in the wild-type C57/BL6J mice in both sexes. Interestingly, the lateralization of the granule cell layer volume was lost in the tfm male mice or in the tfm-carrier females (partially androgen-insensitive), indicating that the lateralization effect in the dentate gyrus of the hippocampus was dependent on the action of androgens in both sexes.

With respect to hemispheric lateralization, some authors tried to relate the different pattern of cerebral functional lateralization to a different connectivity between the hemispheres as a consequence of different exposure to androgens, in particular testosterone, in the early development of the central nervous system in humans and non-human species (Reviewed in Wisniewski, 1998).

A number of animal studies have reported a link between early testosterone exposure and hemispheric specialization (Diamond, 1991; Westergaard et al., 2000).

The two main theories postulating a linkage between foetal testosterone (FT) and neuroanatomical and functional asymmetries in the brain and lateralization in humans are known as the “Callosal Hypothesis” (Witelson and Nowakowski, 1991) and the “Geschwind–Behan–Galaburda Hypothesis” (Geschwind and Galaburda, 1985a,b,c).

According to the "Callosal Hypothesis", increased hemispheric lateralization in males may result from the pruning of callosal axons – partially mediated by testosterone – during foetal and neonatal development. It is suggested, indeed, that increased levels of FT may be related to a greater axonal pruning and in turn to a decreased connectivity and a stronger right-hand preference in men. However, this effect was not observed in women and it was hypothesized that different mechanisms might apply to each sex (Witelson, 1985, 1989). Further support to this theory comes from studies of premature babies showing that babies with very low birth weight (<1000 g) and high prematurity (weeks 26–29) – two factors which may have interfered with normal callosal axonal pruning – were found to be more left-handed (O'Callaghan et al., 1987). Also some authors, using samples of amniotic fluid from normal female foetuses at 16 weeks of gestation, found a correlation between higher FT levels and strong right-handedness and left-hemisphere lateralization for speech at age 10 arguing in favour of the Callosal Hypothesis (Grimshaw, 1995). This theory was also supported by evidence, in post-mortem studies, of a smaller corpus callosum in right-handed men than non-right-handers (Witelson, 1985, 1989). However, these findings have been challenged by other studies. It should also be noted that cross-sectional studies are negatively affected by the enormous variability of the size of the corpus callosum (Giedd et al., 1999). Kertesz et al., based on magnetic resonance imaging, argued with the notion of increased callosal connectivity in left-handers, women or individuals with less-lateralized function, finding that callosal areas did not correlate with brain size or with measures of lateralization for hand performance, dichotic listening or visual field preference (Kertesz et al., 1987). Also recent studies using diffusion-tensor imaging (DTI) and high-resolution morphological MRI revealed a larger total callosal area in right-handed subjects as compared to left-handed subjects and in males as compared to females and an increased anisotropy and diminished diffusion in left-handers, completely contradicting Witelson's proposal (Westerhausen et al., 2004).

With respect to the role of FT in brain lateralization, the second main hypothesis, formulated by Geschwind–Behan–Galaburda (GBG), inferred that FT might cause a slowing in the development of the left hemisphere with a consequent compensatory growth in the right hemisphere, creating a reverse organisation of the cerebral lateralization. That is, left- and right-handedness might be associated with high and low FT levels, respectively. Also a corollary of the GBG model claimed that FT might influence the development of the immune system too, accounting for the associations between immune functioning and laterality (Geschwind and Galaburda, 1985a,b,c).

Although very promising especially for the emphasis on the intra-uterine environment, the GBG hypothesis has also been refuted as subsequent studies failed to support its predictions (Bryden et al., 1994; Obrzut, 1994; Berenbaum and Denburg, 1995). In particular, a study by Gilmore et al. (2007) found the left hemisphere to be *larger* than the right in male neonates in comparison to female neonates, which is exactly the opposite of what would be predicted by the GBG hypothesis.

Foetal Testosterone and Autism

Turning our focus on the neurobiological link between autism and maleness in the light of these two theories – that although criticized, have highlighted the importance of prenatal environmental factors such as male sex hormones on cognitive and psychological brain development – some authors tried to propose a candidate mechanism for the association between maleness and autism just in the role of FT in early brain development (Baron-Cohen et al., 2004).

The "Extreme Male Brain" theory, in fact, argues that prenatal testosterone exposure is a strong candidate for contributing to sexual dimorphism in human behaviour, including social development, and may represent a risk factor for conditions characterized by social impairments, particularly autism spectrum conditions (reviewed in Knickmeyer and Baron-Cohen, 2006).

Indeed elevated FT levels, measured in amniotic fluid, have been positively correlated with a number of autistic traits and inversely correlated with social development and empathy (Knickmeyer et al., 2005, 2006). Indirect evidence in support of this theory comes from a large body of research on the neural and behavioural effects of early exposure to testosterone and its metabolic derivatives both in animal models and genetic disorders causing increased virilization during gestation (Hines, 2006, review).

Hormonal manipulation during critical periods of early life leads to largely consistent outcomes across animal species. Indeed females of both rodents and non-human primates exposed respectively neonatally and prenatally to androgens showed neural and behavioural masculinization (Goy and McEwen, 1980).

Furthermore, studies of individuals with genetically determined prenatal endocrine conditions, such as women with congenital adrenal hyperplasia (CAH) or men with complete androgen insensitivity syndrome (CAIS), provided extensive information on the consequences of prenatal androgen abnormalities.

The prenatal exposure to unusually high levels of testosterone in girls with CAH, a condition characterized by a deficiency of cortisol biosynthesis leading to compensatory increase of ACTH secretion and a shift toward androgens, seems to be linked to increased male typical play behaviours, including increased preferences for toys and activities usually chosen by boys and for male playmates, despite parents encouragement for sex-appropriate behaviours (Hines, 2004; Pasterski et al., 2005). Furthermore, increased autistic traits, as shown by higher scores on Autism Spectrum Quotient (AQ), have been reported in women with CAH, suggesting that prenatal exposure to high levels of testosterone may be involved in vulnerability to autism (Knickmeyer et al., 2006a).

The opposite pattern, with a female-typical psychosexual development, has been shown by men with complete androgen insensitivity syndrome (CAIS), an X-linked disorder characterized by a total lack of functional androgen receptors (Hines et al., 2003; 53; Wisniewski et al., 2000).

Other researchers have looked more directly at the possible link between autism and prenatal and current testosterone. There is evidence that the ratio of the lengths of the second and fourth digit (2D:4D) may be negatively correlated with prenatal

testosterone and smaller 2D:4D ratio has been considered as a "male finger pattern". Some studies found that the 2D:4D ratio of children with autism, their siblings, fathers and mothers were lower than population normative values and suggested that 2D:4D ratio might be a possible marker for autism which could implicate prenatal testosterone in its aetiology (Manning et al., 2001). Although very intriguing, the findings from 2D:4D ratios have not been always consistent, and the results may vary according to the age, race, what is measured, the hand selected and the method used (Manning et al., 2005, 2007; Robertson et al., 2008).

Finally, signs of precocious puberty have been reported in ASD subjects (Tordjman and Ferrari, 1992) and elevated rates of testosterone-related disorders such as polycystic ovary syndrome, irregular menstrual cycle, dysmenorrhoea, hirsutism, severe acne, epilepsy, tomboyism, and bisexuality or asexuality have been found in women with autism spectrum conditions (Ingudomnukul et al., 2007), suggesting post-natal hormone abnormalities in testosterone production or sensitivity, though the relationship between FT and post-natal testosterone levels has not been clarified yet.

Assessment of the effect of testosterone on brain development in humans (and other mammals) is complicated by the fact that there are two different testosterone peaks in males, the first occurring during early gestation, coincident with the period when male testes start to secrete the hormone, the second occurring around birth. Both peaks could have important organizing effects on the male brain.

Adding complexity to the issue, although it is widely held from animal models that testosterone exerts its masculinizing effect on the brain following aromatization into estradiol (as discussed below), recent experiments involving the administration of the non-aromatizable androgen dihydrotestosterone (DHT) to newborn female mice showed that perinatal testosterone exerts masculinizing effects also via androgen receptors (Bodo and Rissman, 2008). In conclusion, clarifying the role of testosterone for brain development appears to be a key goal for autism research and will probably require a large experimental effort in the years to come.

The Role of Oestrogens in Sexually Dimorphic Anatomy and Behaviour

After having considered the role of FT on sexually dimorphic traits and brain lateralization, we now turn our attention to oestrogens.

While sexually dimorphic expression of oestrogen receptors has been consistently reported in areas related to reproductive behaviour, such as the hypothalamus, evidence of sexually dimorphic oestrogen pathways in areas that are not directly related to reproductive behaviour is much more limited. Recent work by Canonaco et al. (2008) suggests the existence of robust sex differences in the expression of oestrogen receptor (ER) α, ERβ and the ER G-protein-coupled receptor 30 (GPR30) in the cerebellum and amygdala of newborn hamsters.

It is important to remember that brain androgen and oestrogen pathways are coupled together, because androgen precursors (androstenedione and testosterone) are converted into oestrogens (oestrone and estradiol respectively) in the brain, by

the cytochrome P450 aromatase enzyme. Thus, it seems, from rodent models, that estradiol, not testosterone, is the true "masculinizing hormone", at least for some brain regions. Many neurons express P450 aromatase, in particular Purkinje cells (Ukena et al., 1998). Indeed, according to this hypothesis, because of the perinatal testosterone surge, the developing male brain is exposed to high levels of oestrogens derived from neural aromatization of testosterone, while the female brain is exposed to high oestrogen levels only after puberty.

The aromatization hypothesis further implies that female rodents might need to be protected prenatally from the effects of the oestrogens produced by the placenta or foetal gonads. It has been interestingly proposed that alpha-fetoprotein (AFP) may play a role in brain sexual differentiation by binding with high-affinity oestrogens produced by the placenta in female rodents. This hypothesis has been tested in the AFP mutant mouse ($AFP^{-/-}$), showing a clear pattern of masculinization and defeminization in the brain and the behaviour of female $AFP^{-/-}$ mice (Bakker et al., 2006).

In agreement with this view, Bakker and Baum suggested that the defeminizing effect of prenatal estradiol in male rodents was avoided in foetal females by a protective role of AFP whereas oestrogens exerted their feminizing action postnatally, as expected, in genetic females (Bakker and Baum, 2008).

However, it should be noted that human AFP does not seem to bind oestrogens although it demonstrated an antioestrogenic activity in oestrogen-sensitive breast cancer (Bennett et al., 2002) and that androgens seem to be the main hormones causing brain masculinization in primate species (Wallen, 2005).

Turning back to the role of oestrogens in sexually dimorphic neuroanatomy, one of the regions examined in neural sexual differentiation studies, the sexually dimorphic nucleus of the medial preoptic area (SDN-POA) – which is involved in many behaviours including masculine sexual and social activities – was found to be five to six times larger in volume in male than in female rats (Gorski et al., 1978). Furthermore it has been found that brief exposure of newborn female rats to very high levels of estradiol masculinizes the volume of the SDN-POA by reducing apoptotic cell death (Arai et al., 1996).

Foetuses and pups seem also extremely sensitive to even low oestrogen doses. For example, it has been found that pregnant mice with deletion of the 5α-reductase gene – exposed for this reason to increased levels of testosterone and, via aromatization, to high estradiol levels during gestation – were characterized by a strongly reduced litter size and foetal loss. Furthermore, administration of an oestrogen receptor antagonist or inhibition of aromatase reversed the high rate of foetal death in the mutant mice, and estradiol treatment of wild-type pregnant mice caused foetal wastage. Taken together, these findings indicated possible oestrogen toxicity during pregnancy (Mahendroo et al., 1997).

In summary, it might be that oestrogen, rather than testosterone, is the critical hormone to understand the skewed sex ratio in autism.

Several studies have begun to dissect out the mechanisms by which oestrogen pathways affect adult behaviour. Oestrogens are well known to exert their effects through two different oestrogen receptors (ER), ERα and ERβ. ERα is thought to be the fundamental receptor-mediating oestrogen action on reproductive organs

and reproductive behaviour, while ERβ is thought to mediate at least some of the effects of oestrogens on behaviours that are not specifically associated with reproduction, such as locomotor activity, arousal, fear responses, anxiety and learning (Krezel et al., 2001). In the same study, ERβ knockout (KO) mice displayed disrupted GABAergic function in the medial amygdala. ERβ appears to be the principal oestrogen receptor expressed in brain areas like the cerebral cortex, the hippocampus and the cerebellum (Bodo and Rissman, 2006). ERα aαnd ERβ have also different functions during brain development, as suggested by the fact that ERβαKO mice show defects of neuronal migration while ERαKOs do not (Wang et al., 2003). Interestingly, a recent genetic study has revealed significant association of the aromatase gene with Asperger syndrome, and the ERβ gene with the Autism Spectrum Quotient (AQ) and the Empathy Quotient (EQ) (Chakrabarti et al., 2009), further underscoring the potential involvement of oestrogen pathways in ASD.

More recently, work by Choleris et al. (2003, 2006) in mice has added a new perspective on the behavioral consequences of developmentally altered oestrogen pathways, proposing the hypothesis that a "gene micronet" made up of ERα and ERβ, oxytocin (OT) and its receptor (OTR) may control development of social cognition. According to this hypothesis, oestrogens act on the oxytocin system in the hypothalamus and in the limbic forebrain, particularly in the amygdala, as suggested by the fact that ERαKO and ERβKO, as well as OTKO female mice, were found to be impaired in social recognition (Choleris et al., 2003, 2006).

Indeed, previous studies on animal models have demonstrated the critical role of OT and the related peptide vasopressin (VP) in stress, coping responses and social, adaptive behaviours influencing social affiliation and social recognition, sexual and maternal behaviours and anxiety and reactivity to stressors (Carter and Keverne, 2002; Pedersen and Boccia, 2006).

Direct effects on human behaviours by OT have also been reported in past researches. In particular OT seems to increase trust in social interaction (Kosfeld et al., 2005) and to reduce responses to social stress (Heinrichs et al., 2003) and intranasal administration of OT improved the ability to infer the mental state of others from social cues of the eye region (Domes et al., 2007), encouraging researchers to explore whether the so-called trust hormone could represent a potential autism treatment (Opar, 2008).

Furthermore, clinical studies on ASD reported lower peripheral levels of OT (Modahl et al., 1998) and higher levels of a precursor form may be less active of OT (OT-X) (Green et al., 2001). Also patients with autism spectrum disorders showed a significant reduction in repetitive behaviours following oxytocin infusion in comparison to placebo infusion (Hollander et al., 2003) and intravenous oxytocin administration has been shown to facilitate retention of social information in those with autism (Hollander et al., 2007). Additional evidence for a link between OT and ASD comes from genetic studies, which associated the gene for the OT receptor (OTR) with autism (Auranen et al., 2002; Shao et al., 2002; Wu et al., 2005).

Noteworthy is that OT and VP expression seems sexually dimorphic in some cases, as cited in the Carter review (2007), with some studies reporting higher OT levels in females versus males and on the contrary enhanced VP function in males as compared to females. Also it seems that intranasal VP administration differentially

affects social communication in the two sexes, promoting agonistic responses in men and affiliative responses in women (Thompson et al., 2006) and that VP exerts a more crucial role in males than females as pointed out by the social impairment displayed in male but not female V1aR-deficient mice (Bielsky et al., 2004, 2005).

Also the functional interactions among OT, reelin and GABA could exert a pivot role to the features of ASD, such that reelin is secreted by specific subtypes of GABAergic interneurons in the adult cortex and hippocampus and a significant reduction in OTR has been observed in heterozygous *reeler* mice (Carter, 2007). Indeed, epigenetic methylation of the reelin or OTR promoter regions induced by developmental events might cause gene silencing and consequent down-regulation of the protein expression.

Oestrogens, Reelin and Cerebellar Circuits

The *Reelin* gene has been implicated in the aetiology of neurodevelopmental disorders such as schizophrenia and autism (Abrahams & Geschwind, 2008; Fatemi, 2005; Keller & Persico, 2003). Interestingly, a common variant of the *Reelin* gene has been found to increase schizophrenia risk only in women (Shifman et al., 2008), confirming that gene–sex interactions can be important for neurodevelopmental disorders.

We have recently begun to assess the interaction between reelin and sex hormones through topical administration of estradiol into the cisterna magna over the cerebellum in newborn mouse pups (Biamonte et al., 2009). Male heterozygous *reeler* mice (*rl*/+) show a decreased number of Purkinje cells (PC) in the cerebellum at post-natal day 15 (P15), while female *rl*/+ mice do not show any PC loss. This represents an interesting example of gender-dependent modulation of phenotypic expression of a mutation in the hemizygous state, whereby males are affected while females are not. What is the reason for this sex-dependent phenotypic expression of the *rl* allele? Starting from the hypothesis that this phenomenon could be mediated by differential exposure to androgen/oestrogens during foetal or early post-natal development, we have shown that pharmacological treatments with the oestrogen receptor agonist 17-β-estradiol (17β2) at P5 into the cisterna magna of mice increase PC numbers in male *rl*/+ but have no effect in female *rl*/+ or male/female wild-type (wt) mice. Conversely, treatments with the oestrogen receptor antagonists tamoxifen or ICI 182780 decreased PC number in wild-type and *rl*/+ females, but did not affect male's PC numbers (Biamonte et al., 2009). Interestingly, in Reelin-null mice (*rl/rl*) PC loss is not affected by gender nor are PC numbers changed by 17-β-estradiol. RT-PCR analysis indicated that heterozygosity leads to a 50% reduction of reelin mRNA in the cerebellum in both sexes, and that 17β-E up-regulates reelin mRNA, particularly in rl/+ males; reelin mRNA upregulation is associated with an increase of all major reelin isoforms. These results, together with data on the levels of androgens and oestrogens in the mouse cerebellum during early post-natal development, suggest that the local androgen/oestrogen ratio can modulate the phenotypic expression of the Reelin mutation in the heterozygous state. In humans, reelin alleles associated with low levels of gene expression may interact with

variable perinatal levels of neuroactive steroids, leading to gender-dependent differences in genetic vulnerability.

Furthermore longitudinal behavioural analysis in these mice evidenced a genotype-by-estradiol interaction for number of ultrasonic vocalizations (USV) in response to separation from the mother at P7. Basal levels of USV in *rl*/+ females were significantly lower than in wild-type females. Estradiol reverted this profile. Also in the homing test on P9, a significant lower percentage of *rl*/+ mice reached the nest area than corresponding wild-type pups. In the absence of motor changes, this indicates a genotype-dependent alteration in sensitivity to or in central processing of social stimuli. Remarkably, also this deficient profile was reverted by neonatal estradiol treatment. When adult male mice were assessed in an attentional set-shifting task, involving the formation of new rules to obtain a palatable reward, *rl*/+ subjects showed a higher number of perseverative responses. Neonatal estradiol abolished the differences between *rl*/+ and wild-type mice (Laviola et al., 2008).

Taken together, these anatomical and behavioural observations support the male *rl*/+ mouse as a model to assess the complex interactions between genetic risk, altered sex hormone levels and a specific neural circuit (the fronto-cerebellar loop) that is relevant for ASD.

Concluding Remarks: Making Sense of the Complexity

Some of the most prominent biological candidates involved in autism – interacting between each other and influenced by sex steroids – include, among others, neuropeptides such as oxytocin and arginine–vasopressin, neurotransmitters like serotonin and GABA, and neurosecretory proteins such as reelin. Testosterone and related steroids and in particular the estradiol/testosterone ratio may play an important role through their receptors in several hormone-sensitive neural regions interacting with many biological factors and influencing patterns of programmed cell death, neurochemical processes, and neural connectivity between brain regions. The cerebellum and the amygdala are emerging as two brain regions where the interplay between genetic risk factors and neurosteroids could turn out to be crucial for autism. In autism research, there is presently a strong need for robust experimental models that should be taken into account the complex interactions between genes, specific neural circuits and the environment.

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