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Review

Sex differences in animal models of schizophrenia shed light on the underlying pathophysiology

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ABSTRACT

Sex differences in schizophrenia are apparent in almost all features of the illness, from incidence and mean age of onset to symptomatology, course of illness and response to pharmacological treatments. Understanding how men and women with schizophrenia differ provides significant clues into the pathophysiology of the disorder. Animal models are powerful tools when dissecting the molecular biology which underlies behavioural disturbances, and allow structured comparisons of biological sex differences without the social environmental gender influence that so often confounds human sex comparison studies. This review will provide a summary of sex differences described in developmental, genetic and drug-induced animal models of schizophrenia and will link sex-specific molecular and behavioural phenotypes of these models in an attempt to unravel the role that sex plays in the pathophysiology of schizophrenia. Both sex and stress hormones interact to shape the developing brain and behaviour and animal models of schizophrenia that include both sexes provide significant insight into the complexities of these interactions and can direct toward novel therapeutic strategies.

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1. Introduction

1.1. Sex differences in incidence and age of onset

The overall incidence of schizophrenia is slightly higher in males, 1.4:1 (McGrath et al., 2008), however this is dependent upon the age groups assessed; at 15–25 years of age the ratio is 2:1, while the incidence is equal at 25–35 years and then switches at 40 years to 1:2 (DeLisi et al., 1989). This can be accounted for by the sex differences in age of onset. Over a century ago, Kraepelin was the first to show that first-time hospitalization for schizophrenia occurs at a younger age in men than in women (Kraepelin, 1909; Markham, 2012). This has been the most replicated finding in studies of gender differences in schizophrenia and includes a series of large-scale epidemiological studies by Häfner and others (Häfner et al., 1991, 1993; Castle et al., 1998). A significant difference in age of onset between the sexes was reported, with a peak onset age of 15–24 in men and 20–29 in women. It has been proposed that the physiologically higher levels of estradiol in young fertile women contribute to the later age of onset of schizophrenia in women as compared to men (Seeman, 1983; Seeman and Lang, 1990). Indeed, early age of menarche has been associated with later age of onset of schizophrenia in women, while no significant correlation was found between puberty and disease onset in men (Cohen et al., 1999). Furthermore, women were found to have a second peak of onset after age 45, and this corresponds with the emergence of menopause and the associated rapid decline of estradiol levels (Riecher-Rössler et al., 1997). Female sex hormones thus appear to delay the age of onset in schizophrenia and may provide an overall functional protection against occurrence of the illness.

1.2. Sex differences in symptom domains and severity

Clinically, several reports suggest sex differences in symptom presentation and course. Traditionally, women were shown to express more affective symptoms such as mood disturbances (Walker et al., 1985; Goldstein, 1988; Szymanski et al., 1995; Koster et al., 2008), and a large scale, epidemiological, population-based study from Australia found that women more commonly presented with depressive symptoms, which tended to persist throughout the course of the illness (Morgan et al., 2008). Females also tend to present with more auditory hallucinations and persecutory delusions (Goldstein and Link, 1988; Rector and Seeman, 1992; Leung and Chue, 2000), although if positive symptoms were grouped together as an overall score this sex difference was lost (Abel et al., 2010). Males, however, consistently express more negative symptoms upon first presentation (Abel et al., 2010) and cognitive deficits (Leung and Chue, 2000). Data from a number of studies described poorer performance in men with schizophrenia on attention, language and executive function compared to women with schizophrenia (Goldstein et al., 1994, 1998; Seidman et al., 1997; Hoff et al., 1998). Females with schizophrenia have also been shown to outperform males with schizophrenia in verbal learning and memory tasks (Bozikas et al., 2010). However, others have found no sex difference in cognitive functioning (Goldberg et al., 1995; Moriarty et al., 2001), or other symptom groups (Lindstrom and von Knorring, 1994; Addington et al., 1996; Larsen et al., 1996; Hayashi et al., 2002).

Cognitive decline begins in the prodromal stages with deficits in speed-of-processing, visual-learning and social-cognition in prodromal individuals (Corigliano et al., 2014). In addition, cognitive functioning is highly associated with functional outcome in schizophrenia (Green et al., 2004). In line with the poorer performance identified in cognitive function, and earlier age of onset, males also show poorer premorbid functioning (Leung and Chue, 2000). Overall, men seem to fair worse than women and have a more severe course of illness, and this is thought to be due to the earlier age of onset (Abel et al., 2010). Women tend to respond better to antipsychotic treatments, and require lower doses than men, however this is dependent upon the type of antipsychotic, menopausal status and disease progression (Abel et al., 2010). However, the functional mechanisms underlying these sex differences apparent in symptomology, age of onset and treatment response remain unclear in human studies. Here animal models provide clues to these fundamental questions on the pathophysiology of schizophrenia.

1.3. Animal models of schizophrenia

Although no animal model can replicate all aspects of the complexities of human neuropsychiatric disorders such as schizophrenia, these can be deconstructed into more simplified endophenotypes that embody the major symptom domains (van den Buuse, 2010; Eyles et al., 2012). For example, schizophrenia is characterized by: *positive* symptoms, including hallucinations and delusions; *negative* symptoms, including social withdrawal, and anhedonia; and cognitive impairments. Positive symptoms can be assessed in rodents by analysing the locomotor response to certain psychomimetic drugs which mimic a hyperdopaminergic state. In addition, attentional disruptions are thought to underlie positive symptomology—reflecting a lack of ability to filter irrelevant environmental stimuli. Sensorimotor gating, a measure of attentional filtering, can be measured in humans and rodents using the pre-pulse inhibition of the startle response (PPI) paradigm. Here a weaker pre-stimulus inhibits the startle response of the rodent/patient to a stronger startling stimulus (pulse) – this pre-pulse inhibition is impaired in people with schizophrenia and by psychomimetic drugs (van den Buuse et al., 2005; Javitt and Freedman, 2015). Latent inhibition is a selective attentional task which is disrupted in people with schizophrenia and by psychomimetic drugs (Lubow and Moore, 1959; Baruch et al., 1988; Barak and Weiner, 2011). Latent inhibition, based on the capability of a subject to ignore irrelevant stimuli, is the reduced conditioning to a previously exposed familiar stimulus when presented in combination with a novel stimulus. This can be assessed in rodents by pre-exposing them to a neutral stimulus (e.g. tone) with no consequences, followed by exposure to the neutral stimulus combined with an additional unconditioned stimulus in the form of a light-cued shock. LI is achieved when rodents ignore the neutral stimulus and only respond to the unconditioned stimulus (this is measured by licking and freezing behaviours during the task) (Barak and Weiner, 2011). Negative symptoms can be assessed using social interaction tasks, and sucrose preference tests for anhedonia, and cognitive impairment can be assessed using a wide variety learning and memory mazes (van den Buuse et al., 2005).

Of the many proposed animal models of schizophrenia, this review will focus on a selection of models that show the strongest translational relevance, demonstrating construct validity (neurochemical deficits; e.g. dopamine hyperfunction, reduced parvalbumin), face validity (mimic core behavioural symptoms; hyperlocomotor activity or enhanced drug-induced locomotor activity, disruptions to LI or PPI, reduced social interaction, anhedonia and cognitive impairments) and predictive validity (positive response to antipsychotics) (Jones et al., 2011). We will further breakdown the various rodent models into developmental; genetic; gene × environment; and drug-induced models according to the Schizophrenia Research Forum, Animal models for Schizophrenia Research, register (Koenig and Carpenter, 2015) http://www.schizophreniaforum.org/res/models/default.asp.