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Review

Gender differences in genetic mouse models evaluated for depressive-like and antidepressant behavior

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Abstract:
Depression is a mental disease that affects complex cognitive and emotional functions. It is believed that depression is twice as prevalent in women as in men. This phenomenon may influence the response to various antidepressant therapies, and these differences are still underestimated in clinical treatment. Nevertheless, most of the current findings are based on studies on male animal models, and relatively few of these studies take possible gender differences into consideration. Advancements in genetic engineering over the last two decades have introduced many transgenic lines that have been screened to study the pathomechanisms of depression. In this mini-review, we provide a compendious list of genetically altered mice that underwent tests for depressive-like or antidepressant behavior and determine if and how the gender factor was analyzed in their evaluation. Furthermore, we compile the gender differences in response to antidepressant treatment. On the basis of these analyses, we conclude that in many cases, gender variability is neglected or not taken into consideration in the presented results. We note the necessity of discussing this issue in the phenotypic characterization of transgenic mice, which seems to be particularly important while modeling mental diseases.

Key words:
depression, antidepressants, mice, genetic models, knockout, tail suspension test, forced swim test, gender

Abbreviations: 5HT – serotonin/serotonergic, AH – anhedonia, AR – adrenergic receptor, BDNF – brain-derived neurotrophic factor, DA – dopamine/dopaminergic, DAT – dopaminergic transporter, DBH – dopamine β-hydroxylase, FST – forced swim test, GABA – γ-aminobutyric acid, GAT-1 – GABA transporter 1, GR – glucocorticoid receptor, HPA – hypothalamic-pituitary-adrenal, HET – heterozygous, KO – knockout, LH – learned helplessness, MAO – monoamine oxidase, NA – noradrenaline/noradrenergic, NET – noradrenergic transporter, OFT – open field test, OE – overexpressed, SERT – serotonergic transporter, SSRI – selective serotonin reuptake inhibitors, TST – tail suspension test

Introduction

Depression is a mental disease that affects complex cognitive and emotional functions. The exact molecular mechanisms of depression are still not completely understood. The current hypotheses regarding depression, which constitute the basis of clinical treatment, rely mainly upon the dysfunction of monoaminergic transmission and stress-induced hyperactivity of

hypothalamic-pituitary-adrenal (HPA) system; many epigenetic factors also contribute to depression [47]. The deregulation of other neurotransmitter systems (GABA-ergic, glutamatergic) is also believed to be involved, and neuronal growth factors may also contribute according to the neurotrophic theory of depression introduced by Duman et al. [24]. Sadly, despite the passage of more than 50 years since the discovery of the first antidepressant drug, the effectiveness of these treatments varies from 50–70%, and antidepressants only provide complete remission for 30% of patients [31]. Rodent models have made substantial contributions to improving our understanding of depression and still remain the basic tool to study the pathogenesis of and possible treatments for depression in the preclinical phase. However, the heterogeneous nature and complexity of depression raise many concerns about developing the perfect animal model, and the applicability of these models to humans remains questionable.

Recent studies have again turned their attention to gender differences in the prevalence of psychosomatic disorders. In particular, it is believed that women exhibit higher rates of affective disorders, such as depression and anxiety, while men are more susceptible to behavioral disorders, such as substance abuse and antisocial personality, as reviewed by Hill and Needham [38]. This phenomenon may influence the responses of patients to various antidepressant therapies, and the difference in these responses is still underestimated in the clinical treatment of depression [61]. Nevertheless, most of the current findings are based on studies carried out using male animal models, and relatively few of these studies take possible gender differences into consideration. In this mini-review, we provide a comprehensive list of genetically altered mice utilized in studies of depression and analyze whether gender was considered in the evaluation of the depressive-like and antidepressant phenotypes.

Gender differences in the clinical onset of depression and antidepressant treatment

For many years, women were regarded as more susceptible to mental health problems than men, however, this prejudice barely had adequate support in the medical literature. It is currently believed that depression is twice as prevalent in women as in men [68], although some concerns have been raised about the misdiagnosis of depression in men. Men are usually less likely than women to consult a doctor when their mental health is judged poorly [82]. Definitely, there is gender variability in response to stressful stimuli, and women and men can experience different types of mental health profile, but one should be cautious in generalizing to avoid mixing different psychopathologies [38]. Despite the wide acceptance of the higher female prevalence of depression [39], this point of view is challenged by some researchers. Their skepticism is most likely based on the lack of any constancy in the neuroendocrine stress response between both the sexes [45]. As concluded by Parker and Brotchie, there is a higher-order biological factor (variably determined neuroticism, 'stress responsiveness' or 'limbic system hyperactivity') that principally contributes to the gender differences in some expressions of illness and reflects the impact of gonadal steroid changes at puberty [61]. The incidence of depression in women also varies by life stage, with many interacting factors such as childbearing or cyclic hormonal changes. Additionally, women are characterized by reproductive-specific mood disorders: pre-menstrual dysphoric disorder, depression in pregnancy, postpartal mood disorder and perimenopausal depressive disorder [68].

Nevertheless, there were only few comprehensive clinical studies that examined differential gender effects in response to antidepressant therapies. Some studies suggested that depressed women are more likely to respond to selective serotonin reuptake inhibitors (SSRI) than to tricyclic antidepressants (TCA), but this was not confirmed by Parker et al., who failed to find evidence of women having a preferential response to SSRI medication [62]. There were only evidences that older age was associated with better TCA response and younger age with SSRI response [62]. Further screening performed on a large group of cases revealed that sertraline (a compound belonging to the new generation of SSRIs) was better tolerated than imipramine in the acute treatment of non-melancholic depression in women, but men responded similarly to these drugs [5]. Another multicenter, double-blind clinical trial showed that females in their reproductive period are more responsive to fluoxetine than the noradrenaline tetracyclic antidepressant maprotiline [52]. Other studies considered the menstrual cycle and showed that premenopausal