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Mini-Review

Preclinical Sex Differences in Depression and Antidepressant Response: Implications for Clinical Research

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Women suffer from depression and anxiety disorders more often than men, and as a result they receive antidepressants to a greater extent. Sex differences in antidepressant response in humans have been modestly studied, and results have been controversial. At the same time, preclinical studies on animal models of depression and antidepressant response have provided insights with regard to sex differences that could be useful for the design and interpretation of future clinical trials. This Mini-Review discusses such sex-differentiated findings with regard to the presentation of depression, endophenotypes, and antidepressant response. In particular, men and women differ in symptomatology of depression, and animal models of depression have revealed sex differences in behavioral indices. However, although in experimental studies behavioral indices and models are adjusted to identify sex differences properly, this is not the case in the use of depression rating scales in clinical studies. Accordingly, preclinical studies highlight the importance of sex differences at the baseline behavioral response and the underlying mechanisms that often converge after antidepressant treatment. This is also a neglected issue in human studies. Finally, preclinical research suggests that, in the quest for potential biomarkers for depression, sex should be an important factor to consider. Careful consideration of sex differences in preclinical research could facilitate and ameliorate the design and quality of clinical studies for disease biomarkers and novel fast-acting antidepressants that are so essential for both men and women suffering from depression.

Key words: female; animal models; gender; biological markers; rating scales; clinical trials

The disease burden of neuropsychiatric disorders in the European Union is about 30% in women and 23% in men (Wittchen et al., 2011). The higher burden for women is due to sex differences in the prevalence, symptomatology, and perhaps treatment of these diseases. It is now well known that women develop dementia, anxiety disorders, panic disorder, posttraumatic stress disorder, and major depression more frequently than men, although alcoholism is more frequent in men (Kessler, 2007; Wittchen et al., 2011; Altemus et al., 2014). Although women are much more likely than men to develop many neuropsychiatric disorders and thus receive psychotropic

SIGNIFICANCE

Depression is twofold more common in women than in men, but antidepressant therapy (and often research) does not take gender into consideration. Discovery of novel antidepressants is essential because available drugs require weeks to improve mood and are not effective in all patients. Over the years, preclinical research has provided insights into the presentation of depression in males and females, the relevance of potential biomarkers, and sex differences in antidepressant response with animal models. We propose that such information derived from animal studies could be useful for designing and interpreting clinical studies on novel, gender-oriented antidepressant treatments.

The authors dedicate this Mini-Review to the memory of Emeritus Professor of Pharmacology Z. Papadopoulou-Daifoti.

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drugs (Williams et al., 1995), there is relatively little knowledge on potential sex differences in the pharmacotherapy of these diseases. This is perhaps because of the fact that, until the 1990s, women were underrepresented in clinical trials for new drugs because the menstrual cycle was treated as a confounding factor, and women of childbearing age were excluded because of fear of potential harm to the fetus (Hrdina, 2000; Simon, 2005; Uhl et al., 2007). In 1990, the National Institutes of Health and the U.S. Food and Drug Administration (and later the European Medicines Agency) enacted guidelines for the inclusion of women in clinical trials (Merkatz et al., 1993). However, conflicting results have been reported since then with regard to potential sex differences in antidepressant response, and whether potential sex differences in pharmacokinetics and pharmacodynamics of current antidepressants have true clinical significance remains unresolved (Kokras et al., 2011a). It is widely accepted, however, that antidepressant treatment is far from optimal, and development of faster acting drugs that successfully tackle depression in a greater percentage of patients is required (Berton and Nestler, 2006). Taking into account potential sex differences in the context of developing new antidepressants and designing clinical trials with potential sex differences in mind could facilitate or improve the discovery process. Therefore, this Mini-Review discusses selected findings on sex differences from preclinical studies on depression, focusing on three main themes, disease presentation, endophenotypes, and response to antidepressant treatment, seeking to highlight potential points of interest for future clinical studies.

PRESENTATION OF DISEASE

Experimental data suggest that females are more vulnerable to the detrimental effects of stress on mood- and anxiety-related behaviors (Dalla et al., 2010, 2011; Bale and Epperson, 2015). For instance, in the forced swim test, females often show more depressive-like behavior than males (Drossopoulou et al., 2004; Dalla et al., 2008a; Kokras et al., 2012), but, as noted elsewhere, conflicting results are also consistently reported (Kokras et al., 2015). In a previous study by our group, it was shown that one index (in that case latency to immobility) was more appropriate to describe depressive-like behavior in females than another index (duration of immobility) that was routinely used to describe depressive-like behavior in males (Kokras et al., 2009a). The concept of adjusting behavioral indices to the sex of the animals is not rare. A similar pattern has been reported for the chronic mild stress model of depression, in which various mild stressors alternate for a period of 6 weeks, and a reduction in sucrose intake suggests depressive-like anhedonia (Franceschelli et al., 2014; Kokras and Dalla, 2014). A 1-hr sucrose drinking test, routinely used in most studies, usually produces reliable reductions in males but not in females. In fact, female rats tend to drink more sucrose than males and to show a more erratic decrease in their consumption in 1-hr tests (Dalla et al., 2005, 2008a). However, when sucrose testing is measured during a 24-hr period, a reduction of sucrose consumption is more evident in female stressed rats than in males (Konkle et al., 2003; Xing et al., 2013). This is another example of how behavioral indices must be adapted to reflect the depressive status in both sexes correctly. Different coping strategies in response to stress are consistently reported for male and female experimental animals. For example, in response to controllable footshock stress, female rats respond actively by escaping, whereas males react passively and tend to freeze (Dalla et al., 2008b; Dalla and Shors, 2009). This is not unlike what has been suggested for humans, that men and women exhibit a differential behavioral response to stress, with the traditional flight or fight response being mostly male (Taylor et al., 2000). Experimental observations such as these raise an interesting issue with regard to human studies on depression and antidepressant response. It is known that depressed women present anxiety, somatization, crying, anger, hostility, and increased appetite and weight gain more frequently than men (Frank et al., 1988; Marcus et al., 2005, 2008). On the other hand, men present lower self-esteem and more self-dislike and mental clouding more frequently than women (Zetin et al., 1984). Moreover, sex hormones influence depressive symptoms such as irritability, insomnia, appetite, and general physical wellbeing (Kornstein et al., 2010; Young and Korszun, 2010). In animal models, there are also strong hints that sex-differentiated behaviors can be modulated by hormones. Such an example of a sex-differentiated behavior that depends on hormones was recently described by our group (Kokras et al., 2016; Fig. 1).

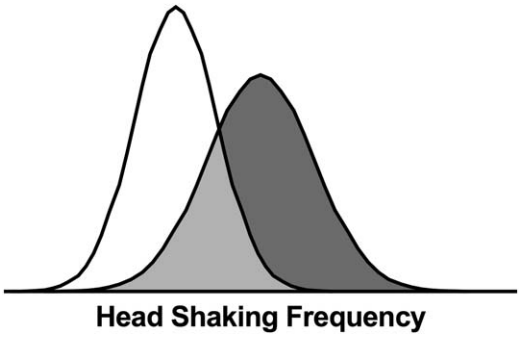

Fig. 1. Male rats (dark gray curve) exhibit a higher head shake frequency than female rats (white curve) in the forced swim test. The sex difference in head shaking behavior has a large effect size (Cohen d = 1,77), and there is an overlap of only 37% (lighter gray area) between sexes in this behavior. Only 6% of male rats are more female-like than the average female, and only 2% of females are more male-like than the average male (data from Kokras et al., 2016; graph based on Maney, 2016).

Despite the well-documented sex differences in preclinical settings and in human studies focusing on sex differences, most clinical drug trials have not shown sex differences at baseline depressive symptoms, at least when

they control for them. This is indeed worrisome because a dearth of experimental and clinical evidence indicates that such differences actually do exist. Furthermore, depression scales such as the Hamilton Depression Rating Scale and the Beck Depression Inventory, routinely used in depression trials, are seemingly and oddly insensitive to sex differences in depression symptoms. Even worse, to the best of our knowledge, the Montgomery-Åsberg Depression Rating Scale, which is the third depression scale routinely used in drug trials, has not been studied at all in relation to sex. In the above-mentioned experimental depression studies, it was not uncommon to adjust behavioral indices to identify the response of each sex correctly. It is surprising that so little research has been devoted to the sex-dependent performance of widely used rating scales and that so little adaptation has been performed to identify correctly the now widely accepted sex differences in stress coping. The goal is to identify those rating scales (equivalent to behavioral indices) that best monitor and track the presentation of depression in men and in women. In many clinical trials, the Hamilton Depression Rating Scale is the gold standard, even though this scale has received significant criticism (Bagby et al., 2004). Adding to that criticism, we find it astonishing that so little research has been performed on its sex-dependent performance and its ability to detect the aforementioned differences in depressive symptoms between men and women, although conflicting evidence suggests that women would score higher than men. In the seminal meta-analysis by Aaron Beck and colleagues (1988) on Beck's scale, the authors noted that, after a number of studies on potential sex differences, results were still conflicting, even though women would probably score somewhat higher than men. Taking into consideration that in clinical trials inclusion criteria often depend on a specific score common for both sexes, if it is true that women score somewhat higher than men, it is possible that women suffering from more severe depression than men have been included/excluded in certain clinical trials. On the other hand, a rating scale insensitive to sex differences in depression symptoms could attenuate the response to a specific treatment that might be more beneficial for men or for women.

ENDOPHENOTYPE AND BIOLOGICAL MARKERS

Several potential biological markers of major depression have been investigated, but none of these has been proved to be sufficiently sensitive and specific to allow inclusion in diagnostic criteria of the disease (Mössner et al., 2007). Among these biological markers, those involving the serotonergic system received considerable attention. These include the platelet binding of antidepressants, which is an indirect index of serotonin transporter activity and activity of several types of serotonin receptors that is studied with neuroimaging or binding and genetic studies. However, there is an abundance of studies strongly indicating that the serotonergic system is highly sex differentiated in its neurotransmission (Dalla et al., 2005; Kokras et al., 2009a), receptors (Drossopoulou et al., 2004; Grippo et al., 2005; Pitychoutis et al., 2012), and transporter (Jovanovic et al., 2008; Olivier et al., 2008). However, the authoritative meta-analysis by Ellis and Salmond (1994) on platelet binding as a biomarker for depression does not mention sex as a potential confounder at all, nor do most studies included in that meta-analysis. Similarly, several neurotrophic factors and mechanisms of adult neurogenesis have been proposed as biological markers for depression. In human studies, brain-derived neurotrophic factor (BDNF) levels and levels of other neurotrophic factors differ between depressed men and women and are associated with duration and severity of the disease (de Azevedo Cardoso et al., 2014; Kreinin et al., 2015). Sex differences in models of depression and in response to antidepressants also occur in adult neurogenesis and BDNF levels (Shors et al., 2007; Hodes et al., 2010; Mahmoud et al., 2016). Furthermore, candidate biomarkers for depression were pursued in inflammatory responses, in which significant sex differences were also identified (Pitychoutis et al., 2009; Pitychoutis and Papadopoulou-Daifoti, 2010). Other proposed candidates include cholesterol, antioxidants, and epigenetic modulations, and, not surprisingly, sex differences are observed in those elements as well (Kamper et al., 2009; Hodes, 2013; Hodes et al., 2015). In light of this evidence, the quest for a biomarker of depression and antidepressant response is likely eluding us because 1) we are not taking sex into consideration or 2) we are not looking for separate biological markers for depression in men and in women. The concept of different biological markers for each sex might seem provocative, but interesting evidence exists in what may be the most studied biomarker, the dexamethasone suppression test (DST). In their meta-analysis, Ribeiro et al. (1993) concluded that the DST serves no prognostic value, without any reference, however, to potential sex differences. Nonetheless, it is widely accepted that the hypothalamic–pituitary–adrenal axis presents significant sex differences, as shown in both experimental and human studies (Young, 1998; Young and Korszun, 2002; Young and Ribeiro, 2006; Kokras et al., 2011b, 2012; Goel et al., 2014), and it was shown that a single DST/corticotropin-releasing hormone test was predictive of treatment response in men but not in women (Binder et al., 2009). Therefore, taking sex into account might improve our understanding of the depression endophenotype and boost research seeking to discover biological markers for the disease and successful treatments.

ANTIDEPRESSANT RESPONSE

Because successful antidepressant treatment has not yet been developed (Berton and Nestler, 2006), the study of current antidepressants in rodent models has received no less attention than the study of baseline experimental sex differences in depression and stress response (Dalla et al., 2010). Most experimental evidence is in agreement that females are more responsive to treatment with tricyclic

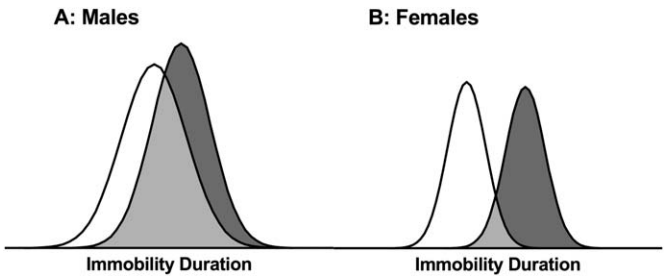

Fig. 2. Male (**A**) and female (**B**) responses to antidepressant treatment in the rat forced swim test. Female rats have a higher response to sertraline than males, as reflected by the reduction of immobility duration (shift of the white curve toward the left of the corresponding darker gray curve). The effect size of antidepressant treatment is $d = 0.87$ for males and $d = 3.01$ for females. In males there is an overlap of 66% (lighter gray area) between vehicle-treated (dark gray curve) and antidepressant-treated (white curve) rats, whereas there is an overlap of only 13% (lighter gray area) between vehicle-treated (dark gray curve) and antidepressant-treated (white curve) females. After treatment, 20% of males still present more immobility than the average vehicle-treated male rat, whereas none of the antidepressant-treated females presents more immobility than the average vehicle-treated female rat (data from Kokras et al., 2015; graph based on Maney, 2016).

antidepressants (Caldarone et al., 2003; Kokras et al., 2009a), selective serotonin reuptake inhibitors (Allen et al., 2012; Kokras et al., 2015; Fernandez-Guasti et al., 2016), and noradrenaline reuptake inhibitors (Gunther et al., 2011). With this in mind, we took note of two other important and closely related observations that arise from our experimental studies. First, we observed that the magnitude of the sex-differentiated antidepressant response was closely dependent on proportional sex differences at baseline, and, second, we observed that, although sex differences were observed at baseline, after antidepressant treatment such differences were often abolished (Leuner et al., 2004; Kokras et al., 2009a,b; Fig. 2). From the human perspective, the data are highly conflicting; most studies have suggested that women have a better outcome when they are treated with selective serotonin reuptake inhibitors (Kornstein et al., 2000; Joyce et al., 2003; Baca et al., 2004; Berlanga and Flores-Ramos, 2006; Young et al., 2009), but other researchers clearly report negative results with regard to sex differences in antidepressant response (Parker et al., 2003; Wohlfarth et al., 2004; Khan et al., 2005). More work is required to clarify this discrepancy. First, in contrast to experimental data, human rating scales poorly reflect sex differences at baseline, as previously discussed. Furthermore, by extrapolating from experimental data, we expect that a successful antidepressant treatment would actually abolish sex differences and thus make it more difficult to detect a difference between men and women. Finally, the controversial concept of "clinical response," defined as an arbitrarily percentage of reduction in a rating scale, has no link to experimental studies or to real-life situations in which full restoration of phenotype (for experimental animals) or full recovery (for real patients) is the actual outcome. At a molecular level, another important issue to consider in depression research is that potential antidepressant compounds acting as exogenous ligands of CNS receptors could be characterized by sex-biased signaling and, therefore, exert differential effects in one sex vs. the other (Valentino et al., 2013). Such differential effects do not necessarily have to reflect different behavioral responses in men and women because in experimental studies the same behavioral endpoint, i.e., the antidepressant response, may come as a result of different underlying mechanisms in males and females (McCarthy et al., 2012). This has been evidenced in experimental animals (Kokras et al., 2009a, 2011b), but, to the best of our knowledge, it has not yet been observed in humans.

CONCLUSIONS

The issues analyzed here are only examples showing how preclinical animal research can provide insights on sex differences relevant to clinical research (Cahill, 2006). Sex differences in depression and antidepressant response might account for some degree of variation in clinical research (Maney, 2016), and understanding its source would improve the process of developing new treatments. Conversely, if clinical researchers are using tools and designs that ignore, attenuate, and correct for potential sex differences, it might be the case that we are missing the discovery of sex-dependent or sex-specific treatments by not conducting sex-aware research (Kokras and Dalla, 2014).

CONFLICT OF INTEREST STATEMENT

All authors declare that they have no conflicts of interest. N.K. has received honoraria and travel support from Janssen-Cilag, Lundbeck, Sanofi-Aventis, Medochemie Generics, and Elpen, S.A. C.D. has received honoraria from Janssen-Cilag and travel support from Boehringer Ingelheim. None of these honoraria is relevant to this Mini-Review.

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