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Sex hormones and immune system: a possible interplay in affective disorders? A systematic review.

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ABSTRACT

Background: Sex hormones and the immune system may play a key role in sex differences in affective disorders. The understanding of their interplay may lead to the detection of new sex-specific tailored therapeutic approaches. The aim of this systematic review is to summarise the evidence supporting a possible association between sex hormones and inflammatory biomarkers in people with affective disorders.

Methods: A systematic search of the literature published until January 2021 was conducted on PubMed database. The initial search identified a total of 1259 studies; 20 studies investigating inflammatory biomarkers and sex hormones in patients exhibiting depressive symptoms were included: 10 studies focused on patients with affective disorders, and 10 studies focused on women in menopause or in the post-partum period exhibiting depressive symptoms.

Results: Testosterone and exogenous female sex hormones may play protective roles through their modulation of the immune system, respectively, in male patients with bipolar disorder and in peri-/post-menopausal women with depression.

Limitations: The main limitations are the paucity of studies investigating both sex hormones and immune biomarkers, the lack of statistical analyses exploring specifically the association between these two classes of biomarkers, and the great heterogeneity between the participants' samples in the studies.

Conclusion: This review highlights the need to investigate the interplay between sex hormones and immune system in affective disorders. The inconsistent or incomplete evidence may be improved

by studies in patients with moderate-high inflammatory levels that specifically evaluate the relationship between sex hormones and the immune system.

Keywords: Sex hormones; Inflammatory biomarkers; Affective disorders; Major depressive disorder; Bipolar disorder; Post-partum depression

INTRODUCTION

One of the most well-known sex differences in affective disorders is the discrepancy between females and males in the prevalence of depression. Specifically, women are twice as likely as men to suffer from depressive symptoms (Albert, 2015; Belmaker and Agam, 2008; Picco et al., 2017), with differences present also in their clinical profile. For example, depressed females show greater number of depressive symptoms, younger age of onset, higher anxiety and higher prevalence of atypical depression in comparison with depressed males. Moreover, female patients show also a later onset of bipolar disorder (BD) with bipolar II/hypomania, higher prevalence of psychotic depression, more family and personal history of suicide and suicide attempts, and more common rapid cycling and mixed episodes (Arnold, 2003; Diflorio and Jones, 2010; Nivoli et al., 2011; Schuch et al., 2014; Smith et al., 2008). Finally, clinical symptoms in major depressive disorder (MDD) differs between sexes, with female patients showing higher prevalence of symptoms like sadness, crying, difficulty in decision making, low energy, irritability, and work difficulties, in comparison with males (Lopez Molina et al., 2014). Remarkably, sex affects the outcome of antidepressant therapies, with differences in response patterns and in side effects (Damoiseaux et al., 2014). In fact, men respond better to tricyclic antidepressants (TCAs) in comparison with women, while women show a better response to selective serotonin re-uptake inhibitors (SSRIs) (Keers and Aitchison, 2010). Unfortunately, even if already in 1993, the US National Institute of Health said that all phase III clinical trials in psychiatry should include women and minority groups (The Lancet, 2016), there is an historical lack of women being enrolled in clinical drug trials, and up until the 1990s, research considered men as an ideal target population, without acknowledging the differences between males and females in treatment response (Liu and Mager, 2016). Today, results remain inconsistent on the sex-modulating effect of antidepressant response, due to differences across studies in

methodologies and criteria used (Sramek et al., 2016). However, sex differences in physiology may affect treatment response in the same way that it affects depression prevalence.

Clearly, sex hormones are obvious factors to be considered in explaining these differences between females and males, and changes in hormone levels during puberty, menstruation, pregnancy and menopause (Sramek et al., 2016) may influence sex differences in depression. For example, the risk of developing depressive symptoms rises in puberty and has been associated with hormonal fluctuations (Studd, 2015), with an increased risk after menarche (DelRosario et al., 2013; Parker and Brotchie, 2010). Moreover, sex hormones are involved also in neural plasticity, with effects on brain structure (e.g., the volume of the hippocampus is affected by both, exogenous and endogenous sex hormones) and cognitive functions (e.g., working memory and executive function) (Barth et a., 2015). Indeed, both oestrogens and progesterone play important roles in the risk of neurocognitive problems (Del Rio et al., 2018), and in mood regulation (Brinton et al., 2008; McEwen and Alves, 1999), while testosterone levels have been implicated in the risk of attempted suicides in BD female patients (Sher et al., 2014).

Differences in sex hormones alone however may not be sufficient to explain sex differences in affective disorders, and equally important might be the role of the immune system in the two sexes (Maes, 1999; Miller and Raison, 2016). Overall, the literature highlights an association between inflammation and changes in motivational state (sickness behaviour) that is comparable with depressive symptoms (e.g., fatigue, sleep disturbances, low mood) (Lasselin et al., 2018; Maes, 1999; Miller and Raison, 2016). Moreover, a subset of depressed patients shows a hyperactivation of the immune system, as indicated by increased levels of pro-inflammatory biomarkers, like C-reactive protein (CRP), haptoglobin, tumour necrosis factor (TNF)-α, and interleukin (IL)-6, IL-3, IL-

12 and IL-18 (Bahrini et al., 2016; Chamberlain et al., 2019; Dowlati et al., 2010; Osimo et al., 2020; Strawbridge et al., 2017). In particular, immune system activation seems to play a significant role in those patients who do not respond to antidepressant treatment, with non-responders showing higher levels of inflammatory markers in comparison with responders, such as CRP, TNF-α, macrophage migration inhibitory factor (MIF), and IL-1β (Cattaneo et al., 2013; Cattaneo et al., 2015; Cattaneo et al., 2020). While the largest study to date as well as the largest meta-analysis of immune biomarkers in depression highlight that, in general, both depressed men and depressed women show increased levels of inflammation (Osimo et al., 2020; Pitharouli et al., *in press*), there is also some initial evidence that the relationship between depression and raised inflammation may have more clinically-significant effects on women than in man: for example Lamers and colleagues have shown that, in the longitudinal Netherlands Study of Depression and Anxiety (NESDA) cohort, higher IL-6 levels predict subsequent chronic course in depressed women but not in depressed men (Lamers et al., 2019). Therefore, investigating differences between the two sexes in the immune response may help in understanding sex differences in patients with affective disorders.

In the general population, females have more innate and adaptive immune cells (Rainville and Hodes, 2019), higher inflammatory marker levels, and higher risk of developing autoimmune disorders, in comparison with men (Quintero et al., 2012; Yang and Kozloski, 2011). Moreover, several studies have shown that menstrual cycle is a risk factor for worsening of symptoms in various inflammation-related chronic diseases, like autoimmune disorders and diabetes, through the action of progesterone and oestrogens on the immune system (Oertelt-Prigione, 2012). Therefore, inflammatory levels may also vary as a consequence of changes in hormone levels (Ford and Erlinger, 2004). Specifically, male sex hormones (androgens) have mainly anti-inflammatory proprieties (Gilliver, 2010), whereas female sex hormones have both pro- and anti-inflammatory

proprieties (Bereshchenko et al., 2018). Nevertheless, the immune regulatory effects of oestrogen depend on several factors, such as immune system activation, reproductive status, concentration of oestrogens, expression of oestrogen receptors (ER-α and ER-β) and/or hypothalamic-pituitary-adrenal (HPA) axis activity (Straub, 2007). For example, both animal and human studies have found that high levels of oestradiol decrease pro-inflammatory cytokine levels in the central nervous system, inhibit pro-inflammatory pathways (e.g., TNF, IL-1β, monocyte chemotactic protein (MCP)-1) and stimulate the production of anti-inflammatory cytokines, (e.g., IL-4, IL-10, transforming growth factor (TGF)-β) (Fairweather et al., 2008; Shivers et al., 2015; Straub, 2007). Indeed, an experimental study in post-menopausal women shows that oestradiol attenuates the production of pro-inflammatory cytokines after endotoxin-induced stimulation (Puder et al., 2001; Straub, 2007), and of course during pregnancy an increase of oestrogen levels is associated with a shift towards an anti-inflammatory profile (Robinson and Klein, 2012). On the contrary, low levels of oestradiol are linked to an increase in pro-inflammatory cytokine levels (e.g., TNF, interferon (INF)-γ, IL-1β) (Benedusi et al., 2012; Straub, 2007).

Taken together, this evidence identifies the interplay between sex hormones and immune system as an exciting new field of investigation that may lead to the understanding of biological mechanisms of affective disorders and to the detection of new tailored treatment strategies. The aim of this systematic review is to investigate the relationship between sex hormones and inflammation in affective disorders by examining studies which measured both sets of biomarkers in the same subjects, together with their mood state. These include patients with affective disorders as well as patients who exhibit depressive symptoms without a clinical diagnosis.

METHODS

Search strategy and eligibility criteria

We searched the literature published until January 2021 on PubMed database using the following search key words and synonyms: ("sex hormones" OR testosterone OR oestrogen OR oestradiol OR androgens OR "gonadal steroid hormones" OR estrone OR E1 OR E2 OR E3 OR progesterone OR "gender differences" OR "sex differences" OR SHBG OR "Sex hormone-binding globulin" OR "luteinizing hormone" OR LH OR "follicle stimulating hormone" OR FSH OR "17 beta oestradiol" OR "free androgen index" OR estriol OR pregnenolone OR allopregnanolone OR aldosterone OR prolactin) AND (inflammation OR cytokines OR interleukins OR "inflammatory biomarker" OR CRP OR "C reactive protein" OR "IL 11" OR "IL 1 β" OR "IL 10" OR "IL 6" OR "TNF" OR "TNF α" OR "interferon") AND ("depression" OR "depressive symptoms" OR "mood disorders" OR "affective disorders" OR "major depressive disorder" OR "psychotic major depression" OR "bipolar disorder" OR "psychosis" OR "bipolar depression" OR "dysthymic disorder" OR hypomanic OR mania OR manic OR "cyclothymic disorder" OR "pre-menstrual dysphoric disorder" OR dysthymia). Studies selected were limited to those written in the English language focusing on human samples. One author screened the abstracts for eligibility (GL) and two authors (GL and CMP) assessed the articles for relevance.

Eligibility of the studies

Specific inclusion criteria included the following:

(1) English language; (2) human studies; (3) adults; (4) at least one sex hormone among oestrogens

and/or androgens measured in blood or saliva and/or at least one exogenous sex hormone administrated; (5) at least one inflammatory biomarker; (6) affective disorder diagnosis or presence of depressive symptoms.

Specific exclusion criteria included the following:

(1) animal studies; (2) review, systematic review, meta-analysis, case report, commentary, editorial; (3) absence of sex hormones measures; (4) absence of inflammatory biomarker analyses; (5) absence of clinical measures; (6) medical and psychiatric comorbidities.

The initial search identified a total of 1259 studies. After removing the duplicates, 5 articles were found through hand-searching and 1096 articles were screened. In all, 1067 studies were excluded, and 29 articles were further investigated for eligibility. Of these, 20 studies investigating inflammatory biomarkers and sex hormones in patients exhibiting depressive symptoms were included. The flowchart of the searching progress is presented in Fig. 1. Specifically, 10 studies focused on patients with affective disorders or affective symptoms, and 10 studies focused on women in menopause or in the post-partum period exhibiting depressive symptoms.

The following studies were found to be eligible and therefore included:

Immune system and sex hormones in affective disorders:

Almeida et al., 2011; Canning et al., 2010; Eisenberger et al., 2009; Haenisch et al., 2015; Keshri et al., 2018; Meier et al., 2018; Miller et al., 1999; Roomruangwong et al., 2020; Shattuck and Muehlenbein, 2015; Suarez et al., 2004.

Immune system and sex hormones in menopause and the post-partum:

Amini et al., 2020; Davis et al., 2006; Figueroa-Vega et al., 2015; Haren et al., 2007; Karaoulanis et al., 2014; Nishi et al., 2020; Okun et al., 2011; Sha et al., 2021; Stephenson et al., 2013; Stojanovska et al., 2015.

RESULTS

Immune system and sex hormones in affective disorders

We found ten studies that measured both inflammation and sex hormones in affective disorders, or healthy subjects with depressive symptoms. A summary of the main results of the studies is shown in Table 1.

Two studies focussing on bipolar disorder found abnormalities in both sets of biomarkers. Specifically, in the study by Haenisch and colleagues (Haenisch et al., 2015), patients in a manic phase showed significantly increased progesterone and insulin (a marker of inflammation) in comparison with controls, and patients with mixed mood state a statistical trend for such increases. In the study by Keshri and colleagues (Keshri et al., 2018), there was a negative correlation between lower testosterone and higher IL-17 levels in BD male patients in remission.

Three studies did not find any significant relationships between sex hormones and inflammatory biomarkers. In the study by Miller and colleagues (Miller et al., 1999), depressed female patients showed higher norepinephrine and oestradiol levels in comparison with female controls, but the

two parameters were not correlated with the immune system measure (lymphocyte proliferative response); interestingly, more severe depressive symptoms on the Beck Depression Inventory (BDI) positively correlated with the number of white cells and granulocytes, indicating an increased immune activity in the more depressed patients. In the study by Meier and colleagues (Meier et al., 2018), oestradiol levels did not correlate with CRP levels in a combined sample of female participants with MDD, BD, and healthy controls; however, women taking oral contraceptives showed lower kynurenine metabolites levels and higher CRP levels in comparison with women not taking contraceptives, and in women taking contraceptives there was a positive correlation between progesterone levels and kynurenine metabolites. Almeida and colleagues (Almeida et al., 2011) found that poor quality of sleep was associated with development of depressive symptoms in older men, but high sensitivity (hs-) CRP and androgen levels were not different across participants with and without sleep problem (and correlations between biomarkers were not presented).

Two studies focused on female subjects with premenstrual syndrome (PMS). The study by Canning and colleagues (Canning et al., 2010) focused the effects of hypericum perforatum in women with PMS. The herbal compound did not affect mood symptoms, inflammatory biomarker or sex hormone levels. However, hypericum perforatum improved insomnia and fatigue. Roomruangwong and colleagues (Roomruangwong et al., 2020) showed that CRP did not change during the menstrual cycle in women with premenstrual syndrome (PMS)/menstrual cycle associated symptoms (MCAS, which include depressive symptoms), although C4 levels were higher in these women, while lipid hydroperoxides (LOOH) was lower; moreover, across multiple time-points in the menstrual factors, higher progesterone correlated with lower LOOH and lower C3, and higher oestradiol with lower haptoglobin.

Two studies focused on cohorts of healthy woman with depressive symptoms. Eisenberger and colleagues (Eisenberger et al., 2009) detected a significant correlation between depressive symptoms and IL-6 in an endotoxin-induced inflammation study. However, controlling for levels of oestradiol and progesterone (as markers of menstrual cycle phase) did not affect the association between clinical symptoms and the inflammatory biomarker. Similarly, in the study by Suarez and colleagues (Suarez et al., 2004), the association between depressive symptom and inflammatory biomarkers (monocyte-associated markers after lipopolysaccharides (LPS) stimulation in vitro) were not influenced by the levels of 17β-oestradiol. The study by Shattuck and colleagues (Shattuck and Muehlenbein, 2015) focused on a cohort of both males and females together; the authors administrated rabies vaccine to healthy subjects, but this did not affect mood, levels of IL-6, cortisol or testosterone.

Immune system and sex hormones in menopause and the post-partum

We found ten studies which focused on mood, sex hormones and inflammatory biomarkers in the post-partum and in peri-/post-menopausal women. A summary of the main results is shown in Table 2.

Three studies investigated administration of *exogenous* sex hormones, together with inflammatory markers and mood, in samples of menopausal women. In one study (Davis et al., 2006), the authors administered transdermal testosterone therapy with latrazole or placebo to women who were already taking transdermal oestrogen therapy. Latrazole is a non-steroidal, reversible aromatase inhibitor (Casper, 2007) that reduces oestrogens levels and induces ovulation (Mejia et al., 2019). Increased testosterone levels after administration of hormonal therapy in post-menopausal women

correlated with an improvement in depressive symptoms, but the authors did not detect significant changes in inflammatory and oestrogen levels. In the study by Haren and colleagues (Haren et al., 2007), serum testosterone and free-androgen index (FAI) correlated with CRP levels and inversely correlates with adiponectin; however, testosterone did not show any significant correlation with neuropsychological function in the whole group, while the sub-group of menopausal women using oestrogen replacement therapy exhibited significantly lower total testosterone and FAI. The study by Stephenson and colleagues (Stephenson et al., 2013) focused on investigating longitudinal associations between transdermal bioidentical hormone combination therapy (BHRT: including oestriol, oestradiol, progesterone, dehydroepiandrosterone (DHEA), and testosterone) in a cohort of post-menopausal women; oestradiol, progesterone levels and their ratio significantly increased, whereas pro-inflammatory biomarkers (matrix metalloproteinase-9 (MMP-9), CRP, fibrinogen) and depressive symptoms significantly decreased.

Three studies investigated *endogenous* sex hormones, inflammatory markers and mood, in (peri-) menopausal women. In the study by Karaoulanis and colleagues (Karaoulanis et al., 2014), there was no significant associations between acute-phase response proteins and depressive symptoms, nor between inflammatory biomarkers and sex hormones. However, the authors highlighted that the use of antidepressants could have affected the association between inflammatory biomarkers and sex hormones, as oestradiol positively correlated with haptoglobin levels in peri-menopausal depressed patients, but only in those women who were not taking SSRIs. In the study by Stojanovska and colleagues (Stojanovska et al., 2015), the use of Lepidium meyenii (Maca, or Peruvian ginseng; a nutritional compound with some antidepressant effects (Brooks et al., 2008)) improved depressive symptoms in a cohort of Chinese post-menopausal women, but the authors did not detect significant differences in oestradiol, follicle stimulating hormone (FSH), thyroid stimulating hormone

(TSH), sex hormone binding globulin (SHBG) and cytokines levels in comparison with placebo group. Finally, the study by Figueroa-Vega and colleagues (Figueroa-Vega et al., 2015) highlighted significant differences between different stages of post-menopause: specifically, late post-menopausal women showed increased BMI and lower oestradiol levels, together with lower CD14+CD11c+ monocytes percentage and higher expression of membrane-bound TNF-α on peripheral CD14+ monocytes, compared with early post-menopausal women; moreover, the whole sample exhibited a positive correlation between log-transformed oestradiol levels and IL-6 levels, although this was partly explained by the positive correlation between oestradiol and body mass index (BMI).

Four studies investigated sex hormones, inflammatory biomarkers and mood in the post-partum. The study by Okun and colleagues (Okun et al., 2011) focused on post-partum affective disorders, but the authors did not detect any significant association between increased risk for recurrent post-partum depression (PPD) and levels of oestradiol, prolactin and cortisol; moreover, even though they did not analyse the correlations between sex hormones and inflammatory biomarkers, an interaction (significant at statistical trend level) between poor quality of sleep and higher IL-6 may have contributed to the recurrence of post-partum depression. The study by Amini and colleagues (Amini et al., 2020) investigated the efficacy of Vitamin D in post-partum depression by focussing on women without a history of depression and who were not taking antidepressants at the time of the trial; although levels of oestradiol and inflammatory biomarker did not show significant changes after treatment, Vitamin D levels were associated with a reduction in depressive symptoms. In the study by Nishi and colleagues (Nishi et al., 2020), pregnant women were randomised to omega-3 polyunsaturated fatty acid (PUFA) or placebo; increased eicosapentaenoic acid (EPA) and oestradiol levels were associated with a decrease in depressive symptoms in the PUFA group, but changes in

oestradiol levels were not associated with changes in hs-CRP, IL-6 and adiponectin levels. In the last study, Sha and colleagues (Sha et al., 2021) did not find differences in sex hormones levels between women with and without post-partum depression, but they found multiple correlations between sex hormones and immune biomarkers: oestrogen positively correlated with IL-6 and negatively with picolinic acid and kynurenine; and progesterone negatively correlated with IL-1β, quinolinic acid, kynurenine/tryptophan ratio, quinolinic/picolinic acid ratio, kynurenine and nicotinamide.

DISCUSSION

To our knowledge, this is the first literature review specifically investigating the triad of factors, sex hormones, inflammation and affective symptoms. However, the paucity of studies investigating our parameters of interest (a total of 20), the lack of statistical analyses exploring specifically the relationship between sex hormones and inflammatory biomarkers, and differences between studies in clinical populations and type of analyses, makes it difficult to reach clear conclusions. A large body of data has investigated either inflammation, or sex hormones, or related biological mechanisms in affective disorders, but only around 2% (20 out of 1096) of the screened articles focused on the *interplay* between inflammation and sex hormones. Of the identified articles, half investigated patients with affective disorders or exhibiting depressive symptoms, and half investigated post-partum and menopausal women. Unfortunately, studies were not designed to address specifically the relationship between sex hormones and inflammation, and thus perhaps the most important conclusion of this systematic review is that such studies are needed.

Most of the studies in patients with depression do not find any correlations between sex hormones and inflammatory biomarkers; however, the studies focussing on BD patients find that higher levels of testosterone and progesterone seem to be associated with lower inflammation in these patients.

In general, BD patients exhibit an altered immune system with higher levels of cytokines in comparison with controls (Bai et al., 2014). In the study by Keshri et al. (2018), male patients with BD in remission show increased pro-inflammatory IL-17 levels and decreased testosterone levels in comparison with controls, with a negative correlation between IL-17 and testosterone (Keshri et al., 2018). These results support the evidence that sees testosterone as an anti-inflammatory agent. In fact, animal studies highlight an anti-inflammatory role of androgens on inflammatory biomarkers (Jia et al., 2015; Kelly et al., 2013), although the opposite direction of association is also possible, that is, that there is an inhibiting role of inflammation on testosterone levels (Tremellen et al., 2018), and an anti- gonadotropic effect of the pro-inflammatory environment (Tomaszewska-Zaremba and Herman, 2009). However, it is important to consider differences between mood states in bipolar disorder. In fact, depressed and manic phases seem to present with different gonadal hormone profile, such as higher testosterone levels in manic episodes than in depressive episodes (Johnson et al., 2013), and these differences between states may also be relevant to the different findings we have in depression (see below). Interestingly, in the study by Haenisch et al. (2015) there are differences in biomarker levels between mixed mood state and manic state. The two clinical sub-groups have higher C-peptide, insulin and progesterone levels in comparison with controls, although for insulin and progesterone the findings in the mixed mood state only reached statistical trend of significance, and interestingly this is also the group with the strongest evidence of immune activation (significantly increased cancer antigen 125, haptoglobin, chemokine CC4 and matrix metalloproteinase-7). Both C-peptide, that is part of proinsulin, and insulin, exert anti-inflammatory

properties (Haidet et al., 2009; Sun et al., 2014; Van Himbergen et al., 2012), thus indicating that higher progesterone levels are associated with lower inflammation in BD (Haenisch et al., 2015). Wooderson and colleagues also detect significantly lower testosterone levels in BD male patients than in healthy male subjects (although, interestingly, the opposite in female BD patients), confirming possible 'protective' effects of testosterone in BD (Wooderson et al., 2015). However, gonadal status of patient needs to be taken in consideration when debating about the protective role of testosterone, as exogenous treatment with testosterone therapy may worse manic symptoms in male patients with hypogonadism (Wong et al., 2009). A comprehensive systematic review investigating BD population highlights differences between patients with psychotic symptoms versus patients without psychotic symptoms, with patients with psychotic symptoms showing lower progesterone levels than BD patients without psychotic symptoms and controls (Buoli et al., 2016).

As mentioned above, the studies focussing on MDD and depressive symptoms do not report significant correlations between sex hormones and inflammatory biomarkers, and do not find a moderating role for endogenous sex hormones in the relationship between inflammatory biomarkers and depressive symptoms. Nevertheless, differences between studies may affect the strength of these conclusions. For example, the study by Meier et al. (2018) shows, in the combined group of female MDD patients, BD patients and controls, that women taking oral contraceptives exhibit higher hs-CRP and lower kynurenine ratios in comparison with women without oral contraceptives (Meier et al., 2018). Because the kynurenine metabolism pathway plays a key role in the transition from chronic inflammation to the development of depressive symptoms by leading to increased levels of neurotoxic kynurenine metabolites (Dantzer, 2016), it is possible to speculate that oestrogens play a protective role in the general female population by exerting anti-

inflammatory proprieties and decreasing kynurenine metabolites. This protective role, however, may be confined to exogenous therapies and not to endogenous hormones, as the study by Miller et al. (1999) shows that depressed women exhibit higher oestradiol levels in comparison with controls and no correlations between oestradiol and inflammatory biomarkers. In the same study, depressed women exhibit higher plasma norepinephrine in comparison with controls, which in theory should exerts an anti-inflammatory action (Feinstein et al., 2002; Marien et al., 2004), but again this was not associated with imune biomarkers (Miller et al., 1999). A similar lack of association between sexual hormones and immune biomarkers is present in the study by Eisenberger et al. (2009) using endotoxin to induce depressed mood in healthy subjects, while the study by Roomruangwong et al. (2020) finds a protective role of progesterone and oestradiol against oxidative stress toxicity (Eisenberger et al., 2009; Roomruangwong et al., 2020), and high oxidative stress is involved in depression (Bhatt et al., 2020).

Why are studies in BD showing some evidence of association between sex hormones and immune function, while studies in depression do not? First, it is important to note that in BD most of the relevant effects are driven by testosterone, and studies investigating testosterone in depression (even without immune biomarkers) are few and influenced by depression subtypes. For example, MDD male patients with atypical features show lower testosterone levels in comparison with MDD male patients with melancholic features (Rodgers et al., 2015). In females, De Wit and colleagues show that depressed female patients have higher levels of free testosterone in comparison with non-depressed subjects (without reaching statistical significance), with no differences in other androgens levels (de Wit et al., 2021). It is also important to highlight that differences in medications between BD and MDD may explain in part the differences we find across studies. For example, female BD patients have higher levels of total testosterone in comparison with female MDD

patients, but the total testosterone levels are associated with the use of valproate in the BD group (Flores-Ramos et al., 2020), and sodium valproate has also been found to inhibit the production of TNF-α and IL-6 in vitro (Ichiyama et al., 2000). Additionally, depressed patients (both males and females) taking SSRI exhibit higher levels of testosterone in comparison with those not taking SSRI (Giltay et al., 2012), and some SSRIs have shown immunosuppressive action (Borsini et al., 2017; Horowitz et al., 2014).

In addition to studies focussing on affective disorders or depressive symptoms, we have also included two groups of conditions in women where sex hormones are considered as directly involved in the mechanisms underpinnings changes in mental health. Menopause can worsen both mental and physical health with the transition towards this phase decreasing the overall quality of patients' life (Llaneza et al., 2012; Blumel et al., 2000). The studies focussing on menopause highlight a possible key role for hormonal therapies as protective factors in peri- and post-menopausal women, possibly through an effect on the immune system.

In the study by Davis and colleagues (Davis et al., 2006), testosterone administration improves depressive symptoms, but without exhibiting a correlation with inflammatory biomarker or oestrogen levels. This is consistent with one study that test similar hypotheses but does not measure hormones levels, and thus do not appear in the core list of papers for our review: Liukkonen and colleagues (Liukkonen et al., 2010) found a correlation between higher CRP and higher depressive symptoms only in women that are not taking exogenous hormones (hormonal replacement therapy or oral contraceptives), indicating again a protective/anti-inflammatory action of hormonal therapy. With regards to exogenous oestrogens, again the study by Stephenson et al. (2013) shows that BHRT improved depressive symptoms with a parallel decrease in pro-inflammatory biomarkers and

increase of sex hormone levels in post-menopausal women (Stephenson et al., 2013). However, different stages of post-menopause, because they have different oestrogens levels, may present different relationship between sex hormones and inflammatory biomarkers. For example, in the study by Figueroa-Vega et al. (2015), late post-menopausal women not only have lower oestradiol levels in comparison with early post-menopausal women, but also present higher inflammation (Figueroa-Vega et al., 2015). This is consistent with the evidence that the use of hormonal therapy may play a protective role in a condition of oestrogen deprivation, from studies in medically ill population. For example, low levels of female sex hormones (i.e., oestradiol and progesterone) are associated with high levels of pro-inflammatory biomarkers (i.e., TNF-α and INF-γ) in a cohort of female patients with relapsing remitting multiple sclerosis (Trenova et al., 2013). Moreover, oestrogens exhibit anti-inflammatory properties in menopausal women at increased risk of developing chronic inflammatory diseases (osteoporosis, atherosclerosis, metabolic diseases) (Villa et al., 2015), although the situation might be different in obesity, as obese female subjects taking oestrogen therapy exhibit a greater risk of showing increased CRP levels (Dixon et al., 2008; Ellulu et al., 2017). Of course, it is also possible that other biological mechanisms may be operating in this context, that are associated with both sex hormones and with immune function. The study by Haren and colleagues focuses on a combined cohort of menopausal and peri-/non-menopausal (Haren et al., 2007), and they found that testosterone, dehydroepiandrosterone sulfate (DHEA-S) and oestradiol show a negative correlation with adiponectin, that is, an adipose tissue-derived hormone with anti-inflammatory proprieties (Ouchi and Walsh, 2007); however, only DHEA-S (and not testosterone or oestradiol) exhibits an independent, negative correlation with depressive symptoms: this suggests a predominant protective role of DHEA-S in this female sub-population, and DHEA is one of the most important precursors of sex hormones.

The picture emerging form the studies focused on post-partum depression is equally uncertain. The study by Okun et al. (2011) does not analyse the associations between sex hormones and inflammatory biomarkers, while the study by Nishi et al. (2020) do not find significant correlations between changes in oestradiol levels and changes in inflammatory biomarkers (Nishi et al., 2020; Okun et al., 2011). The study by Amini and colleagues detects an improvement in post-partum depressive symptoms after Vitamin D treatment, but without any changes in sex hormone and inflammatory levels (Amini et al., 2020), which is surprising, considering that vitamin D has a key role in modulating the immune system (Liu et al., 2018). Only the study by Sha et al. (2020) finds that sex hormones in the post-partum period correlate with immune function: a positive correlation between oestradiol and IL-6, a negative correlation between progesterone and IL-1β, and negative correlations between both sex hormones and kynurenine (Sha et al., 2020). Thus, the authors suggest a pro-inflammatory action of oestradiol and an anti-inflammatory action of progesterone, which is also consistent with the aforementioned evidence that progesterone decreases inflammatory levels during pregnancy (Zhou et al., 2019). Nevertheless, the authors did not find significant differences in sex hormone levels between PPD and non-PDD patients, although it is possible that the entity of drop in sex hormone levels before and after the delivery, and especially of progesterone, may be a major contributor to PPD (Kikuchi et al., 2021); thus, more studies are needed to investigate sex hormones levels during pregnancy (in particular progesterone) and their drop after delivery, with a particular focus on their interplay with the immune system.

LIMITATIONS

The inconsistency in the results of the identified studies may also be due to different immune effects of sex hormones in males and females (female sex hormones in male patients and male sex

hormones in female patients). For example, oestradiol has been shown to have anti-inflammatory effects in neonatal microglia of male rats and pro-inflammatory effects in neonatal microglia of female rats in vitro, with increased IL-1β mRNA response in adult females in vivo (Loram et al., 2012). However, testosterone also has a pro-inflammatory effect in females, as adult mice females show insulin resistance and increased phosphorylation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) p65 after testosterone administration, with a possible role of testosterone in activating NF-κB to induce IL-6 and MCP-1 expression (Su et al., 2017). NF-κB plays an active role in several inflammatory medical conditions, by also stimulating genes encoding for pro-inflammatory cytokines (Liu et al., 2017). Moreover, women with polycystic ovary syndrome (PCOS) show higher levels of pro-inflammatory cytokines, testosterone and greater depressive symptoms in comparison with controls, even though the inflammatory profile does not seem to correlate with mood symptoms nor with testosterone levels (Benson et al., 2008). However, testosterone may inhibit or enhance immune activity according also to menstrual cycle phase and sexual activity (Lorenz et al., 2017).

From a mechanistic point of view, there are of course multiple pathways by which measurable associations between sex hormones and immune measures can affect the brain and mental health. Differences between females and males in affective disorders biology can be due to neuroendocrine mechanisms, growth-factors, neurotransmitters, and metabolic, genetic and stress-related factors, all of which are related to both sex hormones and the immune system (Lohoff, 2010; McGuffin and Rivera, 2015; Strawbridge et al., 2017). For instance, men and women present differences in stress response, with males showing a greater stress reactivity in comparison with females (Kudielka and Kirschbaum, 2005). From a genetic point of view, sex specific genetic variants correlate with increased risk of depression, with female sex, but not male, being associated with variants in PDE4A,

FDX1L, and MYO15B (Kang et al., 2020). Additionally, only women and not men exhibited an association between oestrogen receptor polymorphisms and depression, with ER-α rs2234693 and rs9340799 significantly correlating with risk of late-life depression (Ryan et al., 2011). Genome wide studies (GWS) revealed also sex specific association with single nucleotide polymorphism in depression (Aragam et al., 2011; Lewis et al., 2010). Interestingly, X chromosome carries more genes linked to immune system in comparison with other chromosomes, that may lead to an increased immune response and to autoimmune diseases in women (Brooks 2010).

As mentioned above, studies reviewed here were not designed to address specifically the relationship between sex hormones and inflammation, and did not even select or separate subjects with evidence of at least moderate-high level of inflammation, as indicated by CRP levels equal to or greater than 3 mg/L. Including patients with an hyper-activation of the immune system may be helpful in understanding the interplay between sex hormones and inflammatory biomarkers, and we have recently shown that only depressed patients with CRP greater than 3 mg/L respond to the anti-inflammatory minocycline (Nettis et al., 2021). Higher inflammation is associated with reproductive dysfunction and alterations in the function of the gonadotropin-releasing hormone (GnRH) (Barabás et al., 2020), and with stimulation of aromatase enzymes to convert androgens to oestrogens (Capellino et al., 2014), and thus such effects might only be visible in inflamed depressed patients.

The differences between sexes in inflammatory profiles are also not consistently examined, and when they are, results are inconclusive. For example, in the study by Meier et al. (2018), depressed female patients show higher CRP levels in comparison with male patients (without reaching statistical significance), while females (controls and patients together) show reduced kynurenine metabolites ratios in comparison with males (Meier et al. 2018). In the study by Eisenberg et al.

(2009), higher IL-6 levels significantly correlate with higher depressive symptoms in female but not in male subjects, following an endotoxin-induced inflammatory state (Eisenberg et al., 2009). This inconsistency is in line with the literature: as we have mentioned in the introduction, even if the largest study to date as well as the largest meta-analysis of immune biomarkers in depression show that increased inflammation is present in depression in both males and females (Osimo et al., 2020; Pitharouli et al., *in press*), individual studies have shown inconsistent findings. For example, Ford and Erlinger (Ford and Erlinger, 2004), and Elovainio and colleagues (Elovainio et al., 2009) find correlations between higher inflammation and greater depressive symptoms in men only, while Köhler-Forsberg and colleagues (Köhler-Forsberg et al., 2017) find the same correlation in female depressed patients. Similar sex differences exist in longitudinal studies: for example, the aforementioned NESDA study finds that higher levels of inflammation predict a chronic depression course in women only (Lamers et al., 2019); and Jha and colleagues (Jha et al., 2019) find that, in response to either placebo or sertraline, women with lower CRP at baseline have a greater reduction in depressive symptoms severity compared with women with higher CRP levels, while the opposite is present for men. It is also important to highlight that variations in both sex hormones and immune biomarkers have been demonstrated also in other psychiatric disorders; for example, patients with first-episode psychosis exhibit increased levels of free testosterone (and DHEA-S) (Misiak et al., 2018), while women with psychosis show lower oestradiol levels compared with healthy controls (Huber et al., 2004); and, in post-traumatic stress disorder (PTSD), patients show more severe symptoms and more hospitalisation in the midluteal phase (Bryant et al., 2011). Of course, immune abnormalities have been consistently shown in other psychiatric disorders (Baumeister et al., 2014; Kose et al.,2021; Mondelli et al., 2017; Nettis et al., 2020).

CONCLUSION

In conclusion, while the interplay between sex hormones and immune mechanisms is not clear in the small number of studies on major depressive disorder and post-partum depression, our systematic review highlights a protective, anti-inflammatory role of testosterone in male patients with bipolar disorder, and a protective role of exogenous (rather than endogenous) female sex hormones in specific sub-groups characterised by oestrogen deprivation, such as in peri- and post-menopausal women. However, our understanding of the ways in which sex hormones interact with the immune system in individuals with affective disorders is severely limited by the small number of eligible studies and the lack of comparability across studies. Overall, the inconsistencies in this research so far point to the need for specific studies, designed to understand specifically the interplay between sex hormones and the immune system in individuals with affective disorders, in order to detect new therapeutic strategies. Analysing these two sets of biomarkers will help identifying those patients who may show a better response to a combined treatment with anti-inflammatory and/or hormonal therapies, thus using a precision medicine approach.

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