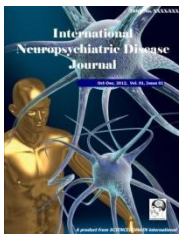

International Neuropsychiatric Disease Journal
2(2): 34-53, 2014

SCIENCEDOMAIN *international*
www.sciencedomain.org

The Involvement of the Hypothalamic-pituitary-gonadal, Hypothalamic-pituitary-adrenal and Somatotrophic Axes in the Development and Treatment of Schizophrenia

T. Gleich[1], J. B. Deijen[1*] and M. L. Drent[1,2]

[1]Department of Clinical Neuropsychology, VU University, Amsterdam, The Netherlands.
[2]Department of Internal Medicine, Section Endocrinology, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, The Netherlands.

Authors' contributions

This work was carried out in collaboration between all authors. Author TG managed the literature searches and wrote the first draft of the manuscript. Authors JBD and MLD revised the first draft, were involved in writing the subsequent drafts and approved the final manuscript.

Review Article

Received 12th September 2013
Accepted 22nd November 2013
Published 13th December 2013

ABSTRACT

In the present review, organizational and activational hormonal effects are proposed to be dysfunctional in schizophrenia and psychosis. Specifically, organizational effects are held responsible for the long-lasting anatomical and functional changes in brain development associated with the disease. Later in life, activational effects may be superimposed and may interact with the earlier induced biological vulnerabilities, eventually triggering the first psychotic episode in schizophrenia. In parallel, it is known that schizophrenia follows a different course in male and female patients and that the first psychotic episode frequently occurs shortly before or during puberty. The different course of schizophrenia in male and female patients seems to be related to digressions in hormonal secretion between the genders. Further the excessive change of hormonal secretion during puberty suggests a relationship between hormonal secretion and the development of schizophrenia, possibly mediated by epigenetic regulation of neuroendocrine systems. We discuss the Hypothalamic-Pituitary-Gonadal (HPG), the Hypothalamic-Pituitary-Adrenal (HPA) and the Somatotropic axes and further present

**Corresponding author: Email: j.b.deijen@vu.nl, jb.deijen@psy.vu.nl;*

evidence for positive treatment effects in schizophrenia by hormonal agents. We conclude that organizational as well as activational effects of hormones may attribute to the development of schizophrenia. Research on hormonal factors in schizophrenia might therefore enhance the general understanding of the disease in regard to its neurobiology and treatment options.

Keywords: Schizophrenia; psychosis; hormones; HPG axis; HPA axis; somatotrophic axis.

1. BACKGROUND

The Hypothalamic-Pituitary-Gonadal (HPG), the Hypothalamic-Pituitary-Adrenal (HPA) and the Somatotrophic axes are important structures maintaining hormonal secretion in humans [1]. The effects of hormonal secretion may be characterized as being organizational or activational. For instance, sex specific characteristics of the human body and brain, known to be programmed during gestation are the consequence of organizational as well as activational processes of hormones secreted by these axes [2]. In general, *organizational processes* reflect permanent anatomical and functional changes as a result of hormonal secretion during brain development. Organizational effects are exemplified by digressions in the size and shape of specific hypothalamic structures in men and women, which may be caused by sex-associated hormonal activity in brain development [1]. In contrast*, activational processes* reflect temporary changes in peripheral and neural processes together with analogous fluctuations in hormonal and cognitive functions. Such short lasting changes are often associated with the time of day, day of the month, season, as well as age. Depending on different hormonal secretion and hormonal effects in men and women, activational effects have also been found to be gender-specific [2].

Organizational and activational processes may also interact. For instance, aggressive behavior in boys may result from the temporal action of testosterone, which is superimposed on its permanent effect on male brain development. Thus, hormones may incidentally be the cause of abnormal brain development, which may be accompanied with distinct direct effects of hormones later in life. In addition, hormone-induced sex-associated differences in cognitive functions are for instance, reflected by the different course in development of schizophrenia in males and females.

The onset of the first signs of schizophrenia and psychosis are frequently reported during puberty, and in 80% of the cases of schizophrenia, the first psychotic episode occurs during the reproductive age [3]. Male schizophrenia patients often experience the first psychotic episode in their early twenties, whereas women develop the first episode during their late twenties [4,5]. Further, there is an increase of schizophrenia-like symptoms after menopause, again an episode in life when strong hormonal changes are present [6,7,8]. Since body and brain undergo gender specific hormonal changes throughout life, hormonal factors may be an underlying cause of the different course of schizophrenia in males and females [9]. Indeed, several studies concluded that it is likely that gender differences during the course of schizophrenia are dependent upon the secretion of sex hormones [10]. Moreover, in some cases psychosis can be completely halted by means of interfering with hormonal factors and thus hormones are frequently held responsible for the exacerbation of psychotic symptoms and might therefore be a causal factor for the development of the disease [11,12]. Thus, altered hormonal secretion and the associated organizational and activational effects may lead to abnormal cognitive development in schizophrenic patients. In

line with this notion is the evidence that baseline hormone levels and number of receptors are deviant in an early phase of schizophrenia [4,13]. The involvement of organizational and activational effects of hormones in schizophrenia and psychosis has already been hypothesized in an earlier study by Seeman and Lang [6]. However, in this study, organizational and activational effects in schizophrenia were only discussed in relation to estrogen and gender differences.

Schizophrenia has been classified by the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) into the schizophrenia subtypes paranoid, disorganized, catatonic, undifferentiated and residual type. The subtypes have been removed in the new DSM-5 because of the limited diagnostic stability, low reliability and poor validity, according to the American Psychiatric Association (APA). As these subtypes had limited use in biological validation studies [14] and are dropped in DSM-5 it seems useless to search for hormonal abnormalities that are specific for these schizophrenia subtypes.

In contrast, attempts have been made to define subgroups of schizophrenia exclusively based on molecular profiles as well as on abnormalities in growth factors and hormones (e.g. follicle stimulating hormones, cortisol, growth hormones etc). It has been reported that schizophrenia patients can be divided into subgroups based on specific molecular and hormonal patterns. Specifically, two distinct subgroups were identified, one group showing predominant changes in immune molecules such as migration inhibitory factor (MIF), interleukin (IL)-8, IL-ira, IL-18 and IL-16. In contrast, the other group showed more changes in growth factors and hormones such as prolactin, resistin, testosterone, insulin, platelet-derived growth factor, leptin and angiotensinogen. There was no association of patients in either group with diagnostic subtypes of schizophrenia [15]. Although research in this area is still in an early phase, this approach seems to be very promising.

In the present review we will address the organizational and activational effects of hormones, including anatomical alterations of the pituitary and hippocampus, in schizophrenia and associated psychosis. As there is no evidence of specific associations between hormonal factors and subtypes of schizophrenia and these subtypes even have been removed from DSM-5 we will not address specific diagnostic subtypes. Although studies on new diagnostic subtypes are warranted, current evidence indicate that hormonal abnormalities may be present in all forms of schizophrenia, likely at a different extent and with specific profiles [15].

The search strategy was based on results of the key terms "schizophrenia, psychosis, hormones,Hypothalamus-Pituitary-Gonadal, Hypothalamus-Pituitary-Adrenal, Somatotrophic axes" on PubMed.com, including only articles in English language.

2. PITUITARY VOLUME

The size of the pituitary gland, which is involved in hormonal regulation and secretion, is found to be increased in medicated schizophrenic patients [16]. Improvement in overall psychotic symptoms in response to medication has also been found to be associated with pituitary volume. Patients at the 25^{th} percentile of pituitary volume (small pituitary volume) are approximately three times more likely to respond to medication than patients at the 75^{th} percentile (large pituitary volume) [17]. In addition to altered pituitary volume there is evidence of basal pituitary-adrenal overactivity, as indicated by higher plasma levels of adrenocorticotropic hormone (ACTH) and cortisol (CORT) in patients during first psychosis and in drug naïve diagnosed schizophrenic patients [18]. Thus, even after controlling for the

effects of medication, pituitary volume and function seems to be abnormal in schizophrenia and acute psychosis.

Other studies indicate that pituitary volume is increased by 10% in schizophrenic patients during their first psychotic episode. However, in established schizophrenia (a duration of at least 5 years) a reduction in pituitary volume of 17% is seen [19]. The authors assume that an increased biological susceptibility to daily life stress or an increased amount of stressors during the first psychotic episode may cause relatively direct alterations in neurochemical factors leading to an increased pituitary size. After several years of chronic hyperactivation of the HPA axis, long term changes such as gluccocorticoid (GC) resistance or sensitization may ultimately lead to a decrease in pituitary volume [19]. Remarkably, also in non-affected relatives of schizophrenic patients pituitary volume was found to be larger than that of controls [20].

As the pituitary gland is almost exclusively involved in hormonal secretion and control, the observed alterations of pituitary volume in medicated and drug-naïve schizophrenic patients are likely related to disturbed neurochemical mechanisms of the HPA axis. In addition, the observed increased pituitary volume in first degree relatives of schizophrenic patients may point to a genetic predisposition mediating organizational effects of stress hormones on brain dysfunction.

3. HPG-AXIS

Puberty is a period in human life wherein hormonal activity and its effects are changing and permanent long-lasting changes in endocrinological variables and brain anatomy are established. During puberty, an increased activation of the HPG axis is observed [21]. The HPG axis is mainly involved in the secretion of the gonadotropin releasing hormone (GnRH), luteinizing hormone (LH), follicle stimulating hormone (FSH), testosterone (T) and estrogen (E) [1].

In puberty the brain is still in a developmental phase, which is likely influenced by hormonal changes. Abnormal organizational processes during puberty may contribute to the biological predisposition for schizophrenia. In addition, subsequent activational effects of gonadal hormones may trigger the occurrence of psychosis.

3.1 Organizational Effects of Gonadal Hormones

High estrogen (E) levels have often been discussed to be a protective factor in schizophrenia, mainly due to the generally lower prevalence of the disease in females. This hypothesis has been discussed as the “estrogen protection hypothesis of schizophrenia” [22,23]. It is also known that in both genders, E is capable of inducing neuronal regeneration and suppressing oxidative stress or glutamatergic cell death [24]. In addition, the protective effect of E is likely mediated via neurotransmitter interactions. E has effects on the dopaminergic system by reducing the amount of D2-receptors and DAT transporters. Thus, E seems to have antagonistic effects on dopamine comparable to the effects of antipsychotics [25].

To investigate whether E could be a causal factor of schizophrenia, early assessment would be necessary. However, assessment of E levels early in life, especially in fetuses is complicated because it could danger the unborn child as well as the mother. Therefore, a

retrospective assessment has been chosen in a study by Procopio, et al. [26]. As the ratio of the length of the index finger to body height seems a valid measure of E concentration in the child during pregnancy, this method was applied [26]. The sample consisted of 119 subjects (27 male controls, 35 male patients, 32 female controls and 25 female patients) between 18 and 65 years, all patients fulfilling ICD-10 criteria for schizophrenia. The results indicated that in female schizophrenia patients a reduced index finger to body height ratio is present. The authors conclude that a relative high concentration of maternal E during pregnancy can probably protect against traumas in utero or at least could limit the damage, while a lower than average concentration of estrogens in utero and/or adult life may be less protective [26].

It is plausible that genetic predispositions may contribute to decreased E concentrations in schizophrenia. In a recent study, the E receptor alpha (ESR1) gene and cortical ESR1 mRNA have been shown to be associated to schizophrenia in case-control genetic association analysis of postmortem brain tissue. Genetic polymorphisms in E specific genes were more frequently observed in schizophrenics of broad ethnic origin compared to controls. Further, 18 ESR1 splice variants and decreased frequencies of the wild-type ESR1 mRNA were detected in schizophrenia [27]. Thus, the variation in the ESR1 gene seems associated with schizophrenia and the mechanism of this association may involve alternative gene regulation and transcript processing [27]. In woman E may mediate the underlying neurochemical and neuropathological abnormalities in schizophrenia and might therefore also be effective in treating the symptoms of schizophrenia [22,23]. Hormonal treatment will be discussed in a later section.

Although it is not clear whether protective effects of E are present in men, there is evidence that other gonadal hormones such as testosterone (T) may be involved in the etiology of schizophrenia in men. This notion is supported by a finding of a study in which male schizophrenic patients (N=54) were assigned to groups with predominant negative and nonpredominant negative symptoms, measured by the Positive and Negative Syndrome Scale (PANSS) [28]. It was found that basal plasma levels of T and free T in schizophrenic male patients with predominant and nonpredominant negative symptoms were significantly lower than those in age matched normal controls. Moreover, plasma levels of FSH and LH in patients with predominant negative symptoms but not in the patients with nonpredominant negative symptoms were found to be significantly lower than in normal controls [28] and a significant inverse correlation was found between the negative symptom scores of the PANSS and plasma levels of free T and T in the subjects with predominant negative symptoms [28]. In a more recent study, decreased levels of active T were found in antipsychotic naive, newly diagnosed schizophrenic patients (N =33) in comparison to a well (for age, sex, body mass index, socioeconomic status and smoking) matched control group (N=33) [29]. In another quite recent study involving 21 male adolescents suffering from prodromal symptoms associated with schizophrenia and 21 non-clinical male controls T levels were determined in saliva. T levels appeared to be significantly lower in adolescents with prodromal symptoms than in non-clinical controls [30]. The observation of low levels of T before the onset of full blown schizophrenia is in line with the hypothesis of abnormal organizational effects of hormones in schizophrenia.

The cited studies suggest a lower baseline level of gonadal hormones in schizophrenic patients and even in patients at high risk to develop schizophrenia. The evidence indicates that in adolescence and adulthood, male and female schizophrenic patient's exhibit reduced levels of respectively T and E while reduced levels of E may already observable in female patients before birth. Although these findings do not proof a direct (causal) relationship

between gonadal hormones and the development of schizophrenia, the observation of subnormal hormonal levels in unmedicated patients and patients at high risk to develop schizophrenia suggests that low levels of gonadal hormones may attribute to the development of the disease.

3.2 Activational Effects of Gonadal Hormones

There are indications for the existence of an activational relationship between E and schizophrenia superimposed on the organizational effects. The role of activational effects of E in the onset of psychosis in schizophrenia has been hypothesized and discussed in earlier studies (e.g. [6]). Further, changes in hormonal factors might contribute to the exacerbation or improvement of psychotic symptoms in general [22,31]. It has also been shown that the high-estrogen luteal phase is associated with significant improvements in psychopathology and functioning in schizophrenic women compared to the low-estrogen follicular phase [22,23]. More evidence of an activational effect of E in schizophrenia comes from life-cycle studies in females. A 20-fold increased risk of suffering a first episode or relapse of psychotic symptoms during the postpartum period of pregnancy was observed when E levels fell dramatically. Further, chronic psychoses may improve during periods in pregnancy when E levels are very high [22,23]. Psychotic women were also found to be more likely to be admitted to a mental institution during a low E phase of their menstrual cycle in comparison to controls [32]. Thus, lower E levels in schizophrenia seem associated with an increased risk of psychotic symptoms. Additionally to the early onset psychosis which often starts around the late 20´s, the onset of psychosis is often seen in postmenopausal women and appears also associated with fluctuations in E during menopause [6,7,8].

It is not clear whether activational effects of E are present in men, although recent studies showed that E might play a role in male schizophrenia as it might be of value as adjunctive treatment [23]. With respect to T levels, it has been shown that these might be negatively correlated with the negative symptomatology in subgroups of schizophrenia, as lower T levels have been observed in a negative-symptom–dominant schizophrenic group compared to a positive-symptom-dominant group of male schizophrenic patients. Unfortunately, only a relative small group of schizophrenic patients were investigated (N=10). Still, similar results were observed in larger samples in earlier studies, also discussed by [33]. No differences were found for other hormones like estradiol and prolactine [33,34]. However, research on activational effects of T in schizophrenia is scarce.

Taken together, the available evidence suggests that at the HPG axis activational effects may be present in schizophrenia. This notion is based on the observed relationship of E and T fluctuations with psychopathology in schizophrenia, low hormonal levels corresponding with high symptomatology.

4. HPA-AXIS

The HPA axis is a major part of the neuroendocrine system, controlling mood and emotions. In general, a disturbance of the HPA axis is associated with stress related diseases like anxiety disorder, major depressive disorder, alcoholism and post-traumatic stress disorder [35]. In particular GCs, secreted by the adrenal glands, like cortisol (CORT) and their effects on hippocampal size will be discussed in the following sections.

4.1 Organizational Effects of Hormones Secreted at the HPA Axis

While it is known that GC receptors (GRs) are expressed in rat brains around embryonic days 13 and 14, the timing of GR expression in humans is not exactly known [36]. However, during the third week of pregnancy, the rat brain is at a similar state as the developing human brain during the late first and early second trimester of pregnancy [37]. Since psychological stress-induced secretion of CORT cannot be optimally attenuated during the second trimester of pregnancy, women are more vulnerable to environmental stressors in this phase [38]. Interestingly, during the late first and second trimester of pregnancy, maternal environmental stressors (critical life events) increasing HPA activity are also associated with an increased incidence of schizophrenia in the offspring [39]. Multiple authors report that low birth weight, which is associated with hypercortisolism in the mother, is linked to schizophrenia [40].

The idea that the action of hormones may underlie biological vulnerabilities in mental and neurological diseases was discussed by Seckl and termed “foetal programming”. A large part of foetal programming may be related to exposure to GCs or indirectly via environmental stress [39]. In sheep, hypercortisolism in mothers, caused by environmental stress or under nutrition, can lead to reduced brain weight at birth, delaying maturation of neurons, myelination, glia and vasculature, to acute effects upon neuronal structure and synapse formation and to a permanently altered brain structure. Prenatal hypercortisolism may also affect the developing dopaminergic system, a notion which might be important for the understanding of dopaminergic dysfunction commonly observed in schizophrenia and psychosis. Finally, long-lasting changes in HPA functions programmed at birth might be gender specific, a finding which would fit to the differences in the course of schizophrenia between males and females [39].

In other studies, the severity of psychosis and the risk for conversion to Axis I psychotic disorders in adolescent patients at high risk for schizophrenia were predictable by CORT levels one and two years later [21,41]. Full-blown abnormalities in hormonal secretion and its effects have been reported by a number of studies indicating a rise in baseline levels of CORT and other stress hormones in medicated and drug-naïve adult schizophrenia patients [42,43]. Further, support for GR abnormalities in established schizophrenia has been provided by post-mortem studies of brains of schizophrenic patients. It has been observed that GR messenger RNA expression was decreased in schizophrenia, a finding which was explained by down regulation of receptors in response to chronic elevation of stress-hormone levels throughout the lifespan in schizophrenia [44]. However, such post-mortem findings also could have been distorted by the effects of antipsychotic medication, taken during the course of life of the patients.

In summary, based on the above evidence, the second trimester of pregnancy in humans can be considered as a time-window of increased sensitivity to maternal stress for the child. The expression of GRs around the same time suggests that specifically GCs may be a biological factor underlying the increased vulnerability to stress. In general, wide ranging pathology in brains of schizophrenic patients may be attributable to pathology in GCs. This pathology, including altered hippocampal volume, might be considered to be an organizational effect of hormonal activity, which could be genetically predetermined.

4.2 Glucocorticoids and hippocampal volume

The hippocampus is highly involved in the inhibition of the stress response at the HPA axis [35] and binding of stress hormones on GRs at the level of the hippocampus may have genomic (long lasting, organizational) and non-genomic (short-lasting, activational) effects [35]. It has been suggested that GC secretion (also mediated by environmental stress) can lead to changes in hippocampal volume, decrease in dendritic spine density and even cell-death. These negative effects of stress on the brain and more specifically on the hippocampus have been investigated in numerous animal studies [45]. It has been shown that repeated doses of corticosterone or environmental stressors can cause thinning and loss of pyramidal neurons in hippocampal area CA3 in vervet monkeys and rats. However, these effects were observed to be reversible within 7-14 days after occurrence of the stressor or corticosterone admission [46,47]. More recent studies in laboratory animals indicate that after chronic stress GCs impair neurogenesis, induce atrophy of dendritic processes and have a neurotoxic effect on the hippocampus [48].

With respect to humans, Cushing's syndrome, a disease which is associated with increased cortisol secretion as well as psychotic symptoms, has been found to be accompanied by reversible bilateral decrease in hippocampal volume [48]. GCs are therefore assumed to be plausible contributors to the atrophy in the hippocampus, particularly given that "the extent of hypercortisolism predicts the extent of atrophy while the extent of recovery from hypercortisolism predicts the extent of volume recovery" [48].

However, a critical review of the notion of the detrimental effects of GCs on the hippocampus has clarified this issue in more detail. In this review the effect of GCs on distinct receptors is assumed to influence cell birth, cell death and probably also cell differentiation. Activation of GRs may lead to hippocampal cell death while activation of mineralocorticoid receptors (MRs) may trigger neuroprotective mechanisms counteracting the cell death. MR occupation appears to be essential for the survival of existing and newly generated neurons. Thus, this duality of receptor types is important for hippocampal cell fate, GR being a promoter of cell death and MR a mediator of cell survival. More specifically, it is assumed that activation of GR can induce loss of neurons in the absence of MR activation while usually the effects only involve dendritic atrophy and loss of synaptic contacts [49] Opposed to the findings showing a negative association between hippocampal volume and basal cortisol levels, as reported by Sapolsky [45,48], a study in healthy male volunteers did show that larger hippocampal volume was associated with higher cortisol levels. In this study the cortisol response to awakening (CRA) over four weeks and the cortisol response to a psychosocial stress task was determined in healthy young (age range 19 – 32 years) males. It appeared that subjects with larger hippocampal volumes showed a greater increase in cortisol in response to stress and to awakening than subjects with smaller hippocampal volumes [50]. The authors indicate that their measurement of reactive cortisol levels instead of diurnal cortisol levels may lead to different results. In addition, they explain the results assuming that in a young, healthy population both a pronounced cortisol response to stress and awakening; along with a large hippocampus may be part of a healthy HPA system, reflecting a successful adaptation to short-term stress.

Opposite to this finding in healthy young subjects, psychosocial and biological stress may lead to a reduced volume of the hippocampus frequently observed in first psychosis schizophrenic patients [47]. High levels of prenatal maternal stress are associated with increased HPA activity being a high-risk factor for the development of schizophrenia in the offspring later in life. Especially critical life events that may lead to an increase of stress

hormone release, such as natural and man-made disasters, prenatal infections or death of a loved one are associated with schizophrenia-like symptoms and anatomical changes in the brain of the offspring [51-53].

Hippocampal size in patients at high risk for psychosis appears to be intermediate in volume between that of healthy controls and diagnosed schizophrenic patients [54]. This finding points to the possibility that hippocampal abnormalities are present early in the course of the disease when full blown symptomatology is still absent [54]. Moreover, post-mortem studies indicate a reduced hippocampal cell size and spine density in brains of schizophrenic patients [55]. Thus, a hypersensitive hormonal stress system due to disinhibition of the HPA axis may be a predisposition to the development of schizophrenia. As a consequence, abnormal high levels of GCs during brain development may alter hippocampal volume and functioning in subjects with a predisposition for schizophrenia.

4.3 Activational Effects of Hormones Secreted at the HPA Axis

As mentioned above, an environmental stressor could trigger schizophrenia-like symptoms if a genetic predisposition for schizophrenia is present. Fluctuations in the secretion of hormones as a response to an environmental stressor can be considered to reflect maladaptive activational effects of hormones, which may be superimposed on the organizational effects.

For example, in four schizophrenic patients, levels of urinary CORT were found to be significantly higher (250%) immediately prior to psychotic episodes, when compared to recovery periods [56]. Thus, intensity as well as frequency of psychotic symptoms in schizophrenic patients appears to be related with long-term fluctuations in CORT [56]. Also other studies have shown a direct relationship between increases in stress hormone levels and the occurrence of psychosis. For instance, the occurrence of psychotic symptoms was found to be associated with Cushing's disease, a state of overproduction of CORT [12,57]. Case reports indicate that there is a remission of psychosis in Cushing's disease with the correction of the hypercortisolemia [12,57]. Thus, by interfering with hormonal factors, psychosis, a main feature of schizophrenia, could be prevented. This is convincing evidence of the high potential of activational effects of stress hormones in the development of psychotic symptoms, commonly observed in schizophrenia. Further, a recent review reported that an enhanced stress response of the HPA axis as well as hypercortisolaemia seem to be evident in subjects at an increased risk to develop schizophrenia-like symptoms such as psychosis [58].

Especially pharmacological challenges such as the dexamethasone suppression test (DST) are often used to investigate HPA axis dysfunction. Dexamemethasone (DEX) is an exogenous gluccocorticoid agonist which leads to suppression of ACTH via the HPA axis negative feedback loop. Thus, administration of DEX leads to suppression of cortisol and is therefore also often used during the diagnosis of Cushing`s disease, as nonsupresssion of cortisol after the administration of the DST is an index of HPA axis dysfunction. In patients with schizophrenia and affective psychosis, higher post-DST levels of cortisol were reported in comparison to healthy controls and depressed patients. Further, antipsychotic treatment often reverses this response [59]. Moreover, schizophrenia patients which do not show a cortisol suppression after administration of the DST had a higher variability on the Brief Psychiatric Rating Scale and more unpredictable clinical outcome than patients showing supression during the DST [60].

Taken together, activational processes of hormones secreted at the HPA axis may play a role in the onset of the symptomatology in schizophrenia. However, the evidence for activational effects of stress hormones presented here are limited. First, most results are discussed in regard to psychosis. Although it is a defining feature of schizophrenia, many other mental diseases are associated with psychosis. Second, some of the findings indicate that the levels of acute secretion and concentration of stress hormones in schizophrenia might be relatively normal. Therefore, it may be assumed that the interaction of activational effects with organizational effects of hormones, exemplified by hypersensibility of the HPA axis, might explain these findings.

5. SOMATOTROPHIC AXIS

The somatotrophic, that is the growth hormone (GH)/ insulin-like growth factor-I (IGF-I) axis is involved in metabolism and the growth of body and brain due to the release and regulation of growth hormone releasing hormone (GHRH), somatostatin (ST), growth hormone (GH), and insulin-like growth factor I (IGF-I) [1]. GH and IGF-I have substantial effects on brain development and body composition; abnormalities in the GH/IGF-I axis may lead to developmental abnormalities [1], which may attribute to a biological vulnerability to schizophrenia.

5.1 Organizational Effects of IGF-I

It has been hypothesized that IGF-I is involved in pre- and post-natal developmental abnormalities in schizophrenia [61]. This is based on the notion that low serum IGF-I levels are related to low birth weight and low IQ in childhood, while low birth weight and low IQ both appear to be related with increased risk of schizophrenia [40]. In a study in antipsychotic-naïve schizophrenia patient's plasma levels of glucose, insulin, IGF-I and cortisol were compared to those of healthy control subjects [62]. The finding that the mean plasma IGF-I level was significantly lower in patients supports the IGF-I deficiency hypothesis as an interpretation of the etiology of schizophrenia. A recent study found a 2-fold decreased serum concentration of GH in a cohort of 236 first and recent onset schizophrenia patients in comparison to 230 matched controls. In addition, GH content was decreased by approximately 1.5 fold in post-mortem pituitaries from schizophrenic subjects (n = 14) compared to controls (n = 15) [63]. IGF-I levels were not determined in this study. It may be suggested that lower activity of the somatrotrophic axis might render the brain more sensitive to neurodevelopmental damage potentially leading to schizophrenia. Since IGF-I receptors are concentrated in the hippocampus, this brain region is likely to be affected due to IGF-I deficits in addition to the detrimental effects of GCs. Moreover, cortisol and IGF-I have been found to be reciprocally related, which became evident in a longitudinal study in schizophrenic patients examining the effect of antipsychotic treatment on IGF-I and cortisol. Following antipsychotic treatment, cortisol levels decreased and IGF-I levels increased. The larger the reduction in cortisol level, the larger the increase in IGF-I level and the larger the improvement in positive symptoms [64]. It may well be true that hypercortisolemia can result in decreased IGF-I levels and that effects of hypercortisolemia on the pathogenesis of schizophrenia might partially be mediated by its inhibitory effects on IGF-I secretion. In turn, decreasing the cortisol levels by antipsychotics might result in significant elevation of IGF-I in schizophrenic patients.

Thus, subnormal IGF-I levels may be a predisposition to the development of schizophrenia. In addition, low levels of IGF-I during brain development may alter hippocampal functioning in subjects with a predisposition for schizophrenia.

6. THE ROLE OF EPIGENETICS IN THE DEVELOPMENT OF SCHIZOPHRENIA

As is clear from the paragraphs above, it has been generally accepted that both genetic and environmental factors (affecting hormonal levels) play a significant role in the pathogenesis of schizophrenia. In some cases, genetic factors alone can be responsible for the development of schizophrenia, while in other cases environmental factors also attribute to the unfolding of the neuropathology.

As environmental factors may rarely being sufficient to cause schizophrenia independently, they are assumed to interact with the underlying genetic liability. However, the pattern of interaction between environmental and genetic factors is still poorly understood. Recent advances in epigenomics have increased the knowledge of this interaction by identifying molecular mechanisms that mediate environmental influences on gene expression and activity, epigenetics being defined as changes in gene expression that occur without changes in DNA sequence [65]. Two of the most widely studied epigenetic changes are DNA methylation and histone modifications [66]. The prenatal erasure and programming of DNA methylation patterns makes the *in utero* time period a window of potential vulnerability for epigenetic dysregulation from environmental exposures, which may be particularly relevant in endocrinology [67]. Another potential vulnerable window for epigenetic dysregulation that might affect endocrine systems include puberty, during which time there is an overall rapid increase in DNA turnover and cell growth [68].

Particularly during embryogenesis genes may epigenetically marked, that mean activated or silenced when epigenetic instructions for ontogenetic development are set in place but also later in life in response to environmental influences [69]. There is increasing evidence that epigenetic mechanisms play a crucial role in mediating the lasting effects of maternal care, stress hormones and nutrition on hippocampal structure and function. For instance, animal studies indicated that early maternal care modulates gene expression resulting in stable patterns of GR expression in the hippocampus and a variable vulnerability to stress in adult offspring [70]. With respect to humans, subjects with histories of abuse manifest increased methylation and decreased expression of hippocampal GRs and long-term vulnerability to stress [71]. Thus, long lasting effects of fetal exposure to hormones like CORT and the availability of nutrients on hippocampal development may be mediated by epigenetic mechanisms [72].

With respect to schizophrenia, prenatal factors that are associated with increased risk of schizophrenia are viral infections, maternal stress and depression, hypoxia and nutritional deficiencies. Postnatal factors, extending from early postnatal period to late adolescence and later include social pathogens like urbanicity, psychological pathogens like stress and chemical pathogens like cannabis use. These prenatal and postnatal factors may increase the risk of schizophrenia by epigenetic misregulation of the liable genome [73]. These epigenetic mechanisms may also mediate the hormonal impact on the development of schizophrenia. When comparing the hormone action within the developing versus the adult brain, it may be true that hormonal exposure during brain development can create lasting epigenetic modifications while hormone exposure in adulthood can have more transient effects on gene expression. However, increasing knowledge of the epigenetic regulation of

neuroendocrine systems suggests that effects of epigenetic modifications are more complex [74].

The current knowledge of epigenetic modulation suggests that prenatal exposure to abnormal levels of cortisol has lasting effects on hippocampal structure and increases the risk of schizophrenia by the mediation of epigenetic mechanisms.

7. HORMONAL TREATMENT IN SCHIZOPHRENIA

In recent years an interrelationship between steroid hormones and dopamine secretion has been shown, suggesting that treatment with hormonal agents may be beneficial in schizophrenia [22,23,75,76]. Traditionally, most of the hypotheses regarding the etiology of schizophrenia are based on dopaminergic abnormalities. Recently, also glutamate and serotonin have been accepted to be involved in the pathophysiology of the disease. As E influences dopaminergic, glutamatergic and serotonergic neurotransmission, its action might influence several neurochemical pathways important in the disease and may have effects similar to atypical antipsychotics [22,23].

Indeed, there is growing evidence that adjunctive therapy with E might play a role in the treatment in schizophrenia, as it might counteract some of the side-effects (like sexual dysfunction) of antipsychotics while having independent properties similar to antipsychotic medication.

In one recent study, 102 women with a psychotic illness were treated by adjunctive treatment with estradiol (100 µg E per day for 28 days). This treatment led to significant improvement in total PANSS scores, positive symptoms, general psychopathology and cognition compared to antipsychotic medication alone [22,23]. E has also been administrated to 14 women with postpartum psychosis, while the Brief Psychiatric Rating Scale (BPRS) was used to evaluate the change of symptoms over time. The psychotic symptoms were reported to decrease within 2 weeks of E treatment. In two patients who discontinued the E treatment, relapse of psychotic symptoms was observed within 2 weeks [63]. Although postpartum psychosis shares main features with schizophrenia, it cannot be considered to be the same disease. Still, it is likely that similar mechanisms attribute to psychosis in postpartum psychosis, as the disease shows high comorbidity with other neuropsychiatric conditions. Currently the antipsychotic effects of E in schizophrenic woman as well as improvement of the neuropsychological performance in response to E treatment have been accepted by many scientists [22,23].

However, it is important to note that treatment with E can be restricted by severe adverse effects, such as breast and uterine change, which may ultimately lead to breast and uterine cancer [77,78]. These kinds of side effects seem to be reduced in patients treated by the highly selective E receptor modulator raloxifene. As this pharmacological agent has E receptor agonist effects in the brain but antagonist effects in breast tissue the risk for the development of uterine cancer is reduced in comparison to patients treated with other E agents. [77].

Recently, the antipsychotic effects of raloxifene as adjunctive treatment to antipsychotic medication were studies in postmenopausal schizophrenic women. The administration of 120 mg raloxifene leads to a significantly more rapid recovery of total and general psychotic symptoms than the administration of antipsychotic medication in combination with a placebo

[77]. Further, significantly greater improvement in total PANSS scores and general psychopathology PANSS scores in comparison to placebo were observed in postmenopausal psychotic women after 12 weeks of 120 mg daily oral raloxifene. Comparable results have been found in other studies [22,23]. Thus, raloxifene seems to show high potential as adjunctive treatment in daily clinical practice.

With respect to the treatment of schizophrenia in men, feminizing effects of E in men may be a reason for restricting treatment. However, the administration of estradiol doses below 2.5mg per day for less than 4 weeks has been found not to induce such side effects in men [79,80,81]. Thus, E has been used as adjunctive treatment in males. For instance, in a placebo-controlled trial in 50 men diagnosed with schizophrenia, 2mg oral estradiol was administrated as an adjunctive treatment to atypical antipsychotics. Participants receiving the estradiol showed a more rapid decline in general psychopathology, which was attributed to increased levels of serum estradiol, as well as to decreased FSH and testosterone. As 28% of the patients receiving treatment did not achieve an increase in serum estradiol, the authors propose further studies in schizophrenic men regarding type, dose and administration route of E [82]. In another recent study, 53 schizophrenic men were adjunctively treated with either 2mg oral E or placebo in a two-week randomized controlled trial. The E group displayed a significantly faster improvement in general psychopathology than the placebo group, and notably, no increase in adverse side-effects were observed [22,23].

Also T has been proposed as adjunctive treatment in schizophrenic men. A randomized, placebo controlled trial in 30 schizophrenic men using 5g of 1% testosterone gel daily additionally to antipsychotic medication lead to an improvement in negative symptoms in patients treated with T as compared to patients treated with a placebo [34].

With respect to steroid hormones, GR antagonists like mifepristone have been hypothesized to have positive effects on symptomatology in schizophrenia. This notion is based on the frequently observed abnormally high levels of GRs and GC concentrations in schizophrenic patients [83]. However, positive effects of treatment with mifepristone in schizophrenia have not been found, suggesting that such treatment might be more beneficial in schizophrenic patients with demonstrable HPA-axis dysfunction than in patients without such abnormalities [83]. Further, as doses were relatively low, studies administrating higher doses are warranted [84]. Treatment of schizophrenic and schizoaffective disorder with the antiglucocorticoid ketoconazole led to reductions in depression but not in psychotic symptoms [85].

In general, as harmful organizational effects of hormones may induce a stable abnormal biological state, short-term hormonal treatment cannot be expected to reduce symptoms of schizophrenia in the long-term. As a consequence, treatment starting early in life may be needed to positively affect organizational processes in the brain, thereby reducing the biological vulnerability to schizophrenia. Such an approach may be exemplified by treatment with GR antagonists during childhood, after GC/GR vulnerability has been diagnosed in the child. However it should be noted that interacting with the hormonal system early in life may have severe maladaptive developmental effects. Nonetheless, it seems important to further increase our knowledge of hormonal drugs that selectively interact with the hormonal system in people in the prodromal phase or early phase of schizophrenia. Eventually with the use of such hormone medication a reduction or even reverse of the biological vulnerability to schizophrenia may be accomplished during the development of the brain.

8. CONCLUSIONS

The present review discusses the available evidence of the involvement of a variety of hormonal factors in the onset and development of schizophrenia. Environmental stressors and genetic predispositions may induce abnormal hormonal processes in the brain of the offspring during pregnancy and adolescence. We believe that genetic predispositions may lead to developmental hormonal abnormalities early in life resulting in an increased risk to develop schizophrenia later in life when strong hormonal changes are present. Further, such abnormalities might independently or in combination with stressful events already be exacerbated during pregnancy and in childhood. These early induced vulnerabilities may represent a causality for schizophrenia as they eventually may lead to an abnormal hormonal regulation, the development of sensitization or resistance of receptors and ultimately to a biological vulnerability to schizophrenia. The long life genetic susceptibility to hormonal influences may be mediated by epigenetic mechanisms. Further, abnormal hormonal processes may damage brain structures and neurons. We further believe that factors causing hormonal abnormalities, such as prenatal maternal stress or genetic predispositions may later in life result in general neurochemical unbalance, as observed in the hormonal and neurochemical abnormalities in schizophrenia and associated psychosis.

In puberty when hormonal levels start to show substantial alterations, the responses of the hormonal system may be disturbed due to the formerly induced developmental abnormalities. As a consequence of the abnormal hormonal responses, structural and functional changes in the pituitary gland and the hippocampus may occur. Disturbance of the hormonal system and structural alterations of the pituitary gland and the hippocampus may be superimposed by phasic hormonal fluctuations that may ultimately trigger the symptoms of schizophrenia. Thus, sub-threshold abnormalities of hormonal levels and receptors may be present in the prodromal phase of schizophrenia and prior to the onset of the first psychosis.

As schizophrenia follows a different course in men and women distinctive hormonal processes in male and females might play a role in the development of schizophrenia. Differences in these developmental processes are mainly observed in relation to gonadal hormones, which are known to play an important role in gender-specific development. It is very likely that these hormones are also related to the gender-specific symptomatology, epidemiology and time-course of the disease.

Since the development of schizophrenia seems to be associated with hormonal changes in pregnancy and puberty, hormones of the HPG axis are the most likely candidates for being the mediators of the maladaptive brain development in schizophrenia. In addition, stress-hormone secretion at the HPA axis could be an additional factor to trigger the onset of schizophrenia and psychosis. A very important contribution to the knowledge of the mechanisms especially involved in organizational effects of hormones on brain development can be provided by studies on the epigenetic regulation of neuroendocrine systems. Current evidence indicates that prenatal exposure to abnormal levels of cortisol can permanently change hippocampal structure and might increase the risk of schizophrenia by the mediation of epigenetic mechanisms. Insight in these epigenetic mechanisms explaining lifelong genetic susceptibility to hormonal influences may provide new treatment strategies.

Altogether, it seems worthwhile to study hormonal abnormalities in schizophrenia, especially in terms of their neuroactive properties and epigenetic modulators. Research on abnormal

hormonal factors in schizophrenia may lead to alternative treatment approaches and may improve the basic understanding of schizophrenia and related mental diseases.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

All authors declare that they have no conflicts of interest.

REFERENCES

1. Gard P. Human Endocrinology. Taylor and Francis, London; 1998.
2. Becker JB, Breedlove SM, Crews D, McCarthy MM. Sex differences in human brain and cognition: The influence of sex steroids in early and adult life. In: Hampson, E., Behavioral Endocrinology (2nd ed.), Cambridge Massachusetts: MIT Press. 2002;579-628.
3. Stevens JR. Schizophrenia: reproductive hormones and the brain. Am J Psychiatry. 2002;159:713-9.
4. Canuso CM, Goldstein JM, Green AI. The evaluation of women with schizophrenia. Psychopharmacol Bull. 1998;34:271-7.
5. Häfner H. Gender differences in schizophrenia. Psychoneuroendocrinology. 2003;28:17–54.
6. Seeman MV, Lang M. The role of estrogens in schizophrenia gender differences. Schizophr Bull. 1990;16:185-94.
7. Riecher-Rössler A, Häfner H, Dutsch-Strobel A, Oster M, Stumbaum M, van Gulick-Bailer M, et al. Further evidence for a specific role of estradiol in schizophrenia? Biol Psychiatry. 1994a;36:492-4.
8. Kulkarni J, Riedel A, de Castella AR, Fitzgerald PB, Rolfe TJ, Taffe J, et al. Estrogen - a potential treatment for schizophrenia. Schizophr Res. 2001;48:137-44.
9. Konnecke R, Häfner H, Maurer K, Loffler W, Van der Heiden W. Main risk factors for schizophrenia: Increased familial loading and pre- and peri-natal complications antagonize the protective effect of estrogen in women. Schizophr Res. 2000;44:81–93.
10. Goldstein JM, Tsuang MT. Gender and schizophrenia: An introduction and synthesis of findings. Schizophr Bull. 1990;16:179–83.
11. Feldman F, Mitchell W, Soll S. Psychosis, Cushing's syndrome and hyperparathyroidism. Can Med Assoc. J. 1968;98(10):508–11.
12. Johnson J. Schizophrenia and Cushing's syndrome cured by adrenalectomy. Psychol Med. 1975;5:165-8.
13. Corcoran C, Walker E, Huot R, Mittal V, Tessner K, Kestler L, et al. The stress cascade and schizophrenia: Etiology and onset. Schizophr Bull. 2003;29:671-92.

14. Korver-Nieberg N, Quee PJ, Boos HB, Simons CJ. The validity of the DSM-IV diagnostic classification system of non-affective psychoses. Aust N Z J Psychiatry. 2011;45:1061-8.
15. Schwarz E, van Beveren NJM, Ramsey J, Leweke FM, Rothermundt M, Bogerts B, et al. Identification of subgroups of schizophrenia patients with changes in either immune or growth factor and hormonal pathways. Schizophr Bull. doi:10.1093/schbul/sbt105
16. Takahashi T, Suzuki M, Velakoulis D, Lorenzetti V, Soulsby B, Zhou SY, et al.. Increased pituitary volume in schizophrenia spectrum disorders. Schizophr Res. 2009;108:114-21.
17. Garner B, Berger GE, Nicolo JP, Mackinnon A, Wood SJ, Pariante CM, et al. Pituitary volume and early treatment response in drug-naive first-episode psychosis patients. Schizophr Res. 2009;113:65-71.
18. Ryan MC, Sharifi N, Condren R, Thakore JH. Evidence of basal pituitary adrenal overactivity in first episode, drug naive patients with schizophrenia. Psychoneuroendocrinology. 2004;29:1065-70.
19. Pariante CM, Vassilopoulou K, Velakoulis D, Phillips L, Soulsby B, Wood SJ, et al. Pituitary volume in psychosis. Br J Psychiatry. 2004;185:5-10.
20. Mondelli V, Dazzan P, Gabilondo A, Tournikioti K, Walshe M, Marshall N, et al. Pituitary volume in unaffected relatives of patients with schizophrenia and bipolar disorder. Psychoneuroendocrinology. 2008;33:1004-12.
21. Walker EF, Walder DJ, Reynolds F. Developmental changes in cortisol secretion in normal and at-risk youth. Dev Psychopathol. 2001;13:721-32.
22. Hayes E, Gavrilidis E, Kulkarni J. The Role of Oestrogen and Other Hormones in the Pathophysiology and Treatment of Schizophrenia. Schizophr Res Treatment. Vol. 2012; Article ID 540273.
23. Kulkarni J, Gavrilidis E, Worsley R, Hayes E. Role of estrogen treatment in the management of schizophrenia. CNS Drugs. 2012;26(7):549–57.
24. Garcia-Segura LM, Azcoitia I, DonCarlos, LL. Neuroprotection by estradiol. Prog Neurobiol. 2001;63(1):29–60.
25. Chavez C, Hollaus M, Scarr E, Pavey G, Gogos A, van den Buuse M. The effect of estrogen on dopamine and serotonin receptor and transporter levels in the brain: An autoradiography study. Brain Res. 2010;1321C:51-9.
26. Procopio M, Davies RJ, Marriott P. The hormonal environment in utero as a potential aetiological agent for schizophrenia. Eur Arch Psychiatry Clin Neurosci. 2006;256:77-81.
27. Weickert CS, Miranda-Angulo AL, Wong J, Perlman WR, Ward SE, Radhakrishna V, et al. Variants in the estrogen receptor alpha gene and its mRNA contribute to risk for schizophrenia. Hum Mol Genet. 2008;17:2293-309.
28. Akhondzadeh S, Rezaei F, Larijani B, Nejatisafa AA, Kashani L, Abbasi SH. Correlation between testosterone, gonadotropins and prolactin and severity of negative symptoms in male patients with chronic schizophrenia. Schizophr Res. 2006;84:405-10.
29. Fernandez-Egea E, García-Rizo C., Miller B, Parellada E, Justicia A, Bernardo M, et al. Testosterone in newly diagnosed, antipsychotic-naive men with nonaffective psychosis: a test of the accelerated aging hypothesis. Psychosom Med. 2011;73(8):643–7.
30. van Rijn S, Aleman A, de Sonneville L, Sprong M, Ziermans T, Schothorst P, et al. Neuroendocrine markers of high risk for psychosis: salivary testosterone in adolescent boys with prodromal symptoms. Psychol Med. 2011;41(9):1815–22.

31. Bergemann N, Parzer P, Runnebaum B, Resch F, Mundt C. Estrogen, menstrual cycle phases, and psychopathology in women suffering from schizophrenia. Psychol Med. 2007;37:1427-36.
32. Huber TJ, Borsutzky M, Schneider U, Emrich HM. Psychotic disorders and gonadal function: evidence supporting the oestrogen hypothesis. Acta Psychiatr Scand. 2004;109:269-74.
33. Goyal RO, Sagar R, Ammini AC, Khurana ML, Alias AG. Negative correlation between negative symptoms of schizophrenia and testosterone levels. Ann N.Y. Acad Sci. 2004;1032:291–4.
34. Ko YH, Lew YM., Jung SW, Joe SH, Lee CH, Jung HG, et al. Short-term testosterone augmentation in male schizophrenics: a randomized, double-blind, placebo-controlled trial. J Clin Psychopharmacol. 2008;28(4):375–83.
35. Lupien SJ, McEwen BS, Gunnar MR, Heim C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nat Rev Neurosci. 2009;10:434-45.
36. Cintra A, Solfrini V, Bunnemann B, Okret S, Bortolotti F, Gustafsson JA, et al. Prenatal development of glucocorticoid receptor gene expression and immunoreactivity in the rat brain and pituitary gland: a combined in situ hybridization and immunocytochemical analysis. Neuroendocrinology. 1993;57:1133-47.
37. Bayer SA, Altman J, Russo RJ, Zhang X. Timetables of neurogenesis in the human brain based on experimentally determined patterns in the rat. Neurotoxicology. 1993;14:83-144.
38. Nierop A, Bratsikas A, Klinkenberg A, Nater UM, Zimmermann R, Ehlert U. Prolonged salivary cortisol recovery in second-trimester pregnant women and attenuated salivary alpha-amylase responses to psychosocial stress in human pregnancy. J Clin Endocrinol Metab. 2006;91:1329-35.
39. Seckl JR. Glucocorticoids, developmental „programming“ and the risk of affective dysfunction. Prog Brain Res. 2008;167:17–34.
40. Gunnell D, Lewis S, Wilkinson J, Georgieva L, Davey GS, Day IN, et al. IGF1, growth pathway polymorphisms and schizophrenia: a pooling study. Am. J. Med. Genet. B. Neuropsychiatr Genet. 2007;144B:117-20.
41. Walker EF, Bonsall R, Walder DJ. Plasma hormones and catecholamine metabolites in monozygotic twins discordant for psychosis. Neuropsychiatry Neuropsychol. Behav Neurol. 2002;15:10-17.
42. Gallagher P, Watson S, Smith MS, Young AH, Ferrier IN. Plasma cortisol-dehydroepiandrosterone (DHEA) ratios in schizophrenia and bipolar disorder. Schizophr Res. 2007;90:258-65.
43. Yilmaz N, Herken H, Cicek HK, Celik A, Yurekli M, Akyol O. Increased levels of nitric oxide, cortisol and adrenomedullin in patients with chronic schizophrenia. Med Princ Pract. 2007;16:137-41.
44. Webster MJ, Knable MB, O'Grady J, Orthmann J, Weickert CS. Regional specificity of brain glucocorticoid receptor mRNA alterations in subjects with schizophrenia and mood disorders. Mol Psychiatry. 2002;7:985-94.
45. Sapolsky RM, Krey LC, McEwen BS. The neuroendocrinology of stress and aging: the glucocorticoid cascade hypothesis. Endocr Rev. 1986;7(3):284–301.
46. Sapolsky RM. Stress, the aging brain and the mechanisms of neuron death. Cambridge, Massachusetts: MIT Press; 1992.
47. McEwen BS, Magarinos AM. Stress effects on morphology and function of the hippocampus. Ann N.Y. Acad Sci. 1997;821:271-84.

48. Sapolsky RM. Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. Arch Gen Psychiatry. 2000;57(10):925–35.
49. Sousa N, Almeida OF. Corticosteroids: Sculptors of the hippocampal formation, Rev Neurosci. 13:59-84.
50. Pruessner M. Pruessner JC. Hellhammer DH. Bruce Pike G. Lupien SJ. The associations among hippocampal volume, cortisol reactivity, and memory performance in healthy young men. Psychiatry Res. 2007;155(1):1-10.
51. Koenig JI, Kirkpatrick B, Lee P. Glucocorticoid hormones and early brain development in schizophrenia. Neuropsychopharmacology. 2002;27:309–18.
52. Rapoport JL, Addington AM, Frangou S, Psych MR. The neurodevelopmental model of schizophrenia: update 2005. Mol Psychiatry. 2005;10;434-49.
53. Sullivan PF. The genetics of schizophrenia. PLoS Med. 2005;2:e212.
54. Lawrie SM, Whalley HC, Abukmeil SS, Kestelman JN, Donnelly L, Miller P, et al. Brain structure, genetic liability, and psychotic symptoms in subjects at high risk of developing schizophrenia. Biol Psychiatry. 2001;49:811-23.
55. Rosoklija G, Toomayan G, Ellis SP, Keilp J, Mann JJ, Latov N, et al. Structural abnormalities of subicular dendrites in subjects with schizophrenia and mood disorders: preliminary findings. Arch Gen Psychiatry. 2000;57:349-56.
56. Sachar EJ, Kanter SS, Buie D, Engle R, Mehlman R. Psychoendocrinology of ego disintegration. Am J Psychiatry. 1970;126:1067-78.
57. Chu JW, Matthias DF, Belanoff J, Schatzberg A, Hoffman AR, Feldman D. Successful long-term treatment of refractory Cushing's disease with high-dose mifepristone (RU 486). J Clin Endocrinol Metab. 2001;86:3568-73.
58. Aiello G, Horowitz M, Hepgul N, Pariante CM, Mondelli V. Stress abnormalities in individuals at risk for psychosis: A review of studies in subjects with familial risk or with “at risk” mental state. Psychoneuroendocrinology. 2012;37(10):1600-13.
59. Holtzman CW, Trotman HD, Goulding SM, Ryan AT, Macdonald AN, Shapiro DI, et al. Stress and neurodevelopmental processes in the emergence of psychosis. Neuroscience. 2013;249:172–91.
60. Mauri MC, Vita A, Giobbio GM, Ferrara A, Dieci M, Bitetto A, Altamura AC. Prediction of response to haloperidol in schizophrenia: neuroendocrine, neuromorphological and clinical variables. Int Clin Psychopharm. 1994;9(1):3–7.
61. Gunnell D, Holly JM. Do insulin-like growth factors underlie associations of birth complications, fetal and pre-adult growth with schizophrenia? Schizophrn Res. 2004;67:309-11.
62. Venkatasubramanian G, Chittiprol S, Neelakantachar N, Naveen MN, Thirthall J, Gangadhar BN, et al. Insulin and Insulin-Like Growth Factor-1 Abnormalities in Antipsychotic-Naïve Schizophrenia. Am J Psychiatry. 2007;164:1557-60.
63. Guest PC, Schwarz E, Krishnamurthy D, Harris LW, Leweke FM, Rothermundt M, et al. Altered levels of circulating insulin and other neuroendocrine hormones associated with the onset of schizophrenia. Psychoneuroendocrinology. 2011;36:1092-6.
64. Venkatasubramanian G, Chittiprol S, Neelakantachar N, Shetty T, Gangadhar BN, et al. Effect of antipsychotic treatment on Insulin-like Growth Factor-1and cortisol in schizophrenia: A longitudinal study. Schizophr Res. 2010;119:131-7.
65. Wolffe AP. Guschin D. Review: chromatin structural features and targets that regulate transcription. J Struct Biol. 2000;129(2-3):102-22.
66. Fleisch AF, Wright RO, Baccarelli AA. Environmental epigenetics: a role in endocrine disease? J Mol Endocrinol. 2012;49(2):61-7. doi: 10.1530/JME-12-0066.

67. Stocker CJ, Arch JR, Cawthorne MA. Fetal origins of insulin resistance and obesity. Proc Nutr Soc. 2005;64(2):143-51.
68. Bjornsson HT, Sigurdsson MI, Fallin MD, Irizarry RA, Aspelund T, Cui H, et al. Intra-individual change over time in DNA methylation with familial clustering. JAMA. 2008;299(24):2877-83. doi: 10.1001/jama.299.24.2877.
69. Morgan HD, Santos F, Green K, Dean W, Reik W. Epigenetic reprogramming in mammals. Hum Mol Genet. 2005;14(1):47-58.
70. Sweatt JD. Experience-dependent epigenetic modifications in the central nervous system. Biol Psychiatry. 2009;65(3):191-7. doi: 10.1016.
71. McGowan PO, Sasaki A, D'Alessio AC, Dymov S, Labonté B, Szyf M, et al. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. Nat Neurosci. 2009;12(3):342-8. doi: 10.1038/nn.2270.
72. Lucassen PJ, Naninck EF, van Goudoever JB, Fitzsimons C, Joels M, Korosi A. Perinatal programming of adult hippocampal structure and function; emerging roles of stress, nutrition and epigenetics. Trends Neurosci. 2013, S0166-2236(13)00138-0. doi: 10.1016/j.tins.2013.08.002.
73. Maric NP, Svrakic DM. Why schizophrenia genetics needs epigenetics: a review. Psychiatr Danub. 2012;24(1):2-18.
74. Auger CJ, Auger AP. Permanent and plastic epigenesis in neuroendocrine systems. Front Neuroendocrinol. 2013;34(3):190-7. doi: 10.1016/j.yfrne.2013.05.003.
75. Sánchez MG, Bourque M, Morissette M, Di Paolo T. Steroids-dopamine interactions in the pathophysiology and treatment of CNS disorders. CNS Neurosci Ther 2010;16(3):e43-71.
76. Doucet S, Jones I, Letourneau N, Dennis CL, Blackmore ER. Interventions for the prevention and treatment of postpartum psychosis: a systematic review. Arch Womens Ment Health. 2011;14:89–98.
77. Kulkarni J, Gurvich C, Lee SJ, Gilber H, Gavrilidis E, de Castella A, et al. Piloting the effective therapeutic dose of adjunctive selective estrogen receptor modulator treatment in postmenopausal women with schizophrenia. Psychoneuroendocrinology. 2010;35:1142-7.
78. Dallal CM, Stone RA, Cauley JA, Ness RB, Vogel VG, Fentiman IS, et al. Urinary estrogen metabolites and breast cancer: a combined analysis of individual level data. Int J Biol Mark. 2012;28(1):3-16.
79. Kirschbaum C, Schommer N, Federenko I, Gaab J, Neumann O, Oellers M, e al. Short-term estradiol treatment enhances pituitary-adrenal axis and sympathetic responses to psychosocial stress in healthy young men. J Clin Endocrino Metab. 1996;81(10):3639–43.
80. Kyomen HH, Hennen J, Gottlieb GL, Wei JY. Estrogen therapy and noncognitive psychiatric signs and symptoms in elderly patients with dementia. Am J Psychiatry. 2002;159:1225–7.
81. Hall KA, Keks NA, O'Connor DW. Transdermal estrogen patches for aggressive behavior in male patients with dementia: a randomized, controlled trial. Int Psychogeriatr. 2005;17(02):165–78.
82. Kulkarni J. de Castella A, Headey B, Marston N, Sinclair K, Lee S, et al. Estrogens and men with schizophrenia: Is there a case for adjunctive therapy? Schizophr Res. 2011;125:278-83.
83. Gallagher P, Watson S, Smith MS, Ferrier IN, Young AH. Effects of adjunctive mifepristone (RU-486) administration on neurocognitive function and symptoms in schizophrenia. Biol Psychiatry. 2005;57:155–61.

84. Schatzberg AF, Lindley S. Glucocorticoid antagonists in neuropsychotic disorders. Eur J Pharmacol. 2008;583:358–64.
85. Marco EJ, Wolkowitz OM, Vinogradov S, Poole JH, Lichtmacher J, Reus VI. Double-blind antiglucocorticoid treatment in schizophrenia and schizoaffective disorder: a pilot study. World J Biol Psychiatry. 2002;3:156-61.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?iid=371&id=29&aid=2716