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Research report

Quetiapine treatment reverses depressive-like behavior and reduces DNA methyltransferase activity induced by maternal deprivation

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ABSTRACT

Stress in early life has been appointed as an important phenomenon in the onset of depression and poor response to treatment with classical antidepressants. Furthermore, childhood trauma triggers epigenetic changes, which are associated with the pathophysiology of major depressive disorder (MDD). Treatment with atypical antipsychotics such as quetiapine, exerts therapeutic effect for MDD patients and induces epigenetic changes. This study aimed to analyze the effect of chronic treatment with quetiapine (20 mg/kg) on depressive-like behavior of rats submitted to maternal deprivation (MD), as well as the activity of histone acetylation by the enzymes histone acetyl transferases (HAT) and deacetylases (HDAC) and DNA methylation, through DNA methyltransferase enzyme (DNMT) in the prefrontal cortex (PFC), nucleus accumbens (NAc) and hippocampus. Maternally deprived rats had a depressive-like behavior in the forced swimming test and an increase in the HDAC and DNMT activities in the hippocampus and NAc. Treatment with quetiapine reversed depressive-like behavior and reduced the DNMT activity in the hippocampus. This is the first study to show the antidepressant-like effect of quetiapine in animals subjected to MD and a protective effect by quetiapine in reducing epigenetic changes induced by stress in early life. These results reinforce an important role of quetiapine as therapy for MDD.

1. Introduction

A wide variety of research shows that the pathophysiology of MDD involves several biological mechanisms both, in the central nervous system and other physiological systems [64]. The low therapeutic responses of classical antidepressants suggest that MDD is an etiologically heterogeneous disorder [21]. Among the various biological and psychosocial factors, stress during childhood history, such as sexual abuse, physical neglect and family violence were correlated with a higher vulnerability to MDD and anxiety in adulthood [14,65]. In addition, childhood trauma has also been associated with poor response to treatment, similarly to treatment-resistant depression (TRD) [41]. Stress in childhood induces changes in the hypothalamic pituitary adrenal (HPA) axis activity [6,22], a classic physiological phenomenon associated to stress [63]. Studies have shown that changes in HPA axis function are found in MDD individuals who have experienced early life stress [1,54].

Despite the changes in the HPA axis functions, which seem inherent or interrelated to other physiological changes, researches have added an intense focus on epigenetic phenomena intricate in the processes that occur along or much later in individuals exposed to stress at the beginning of life. Among other mechanisms, epigenetic includes processes, which are better known and

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more emphasized in the scientific literature, namely: DNA methylation, which mechanism consist in covalent addition of a methyl group at the 5′ position for cytosine residue, through the DNA methyltransferases (DNMT) enzymes, especially when cytosine is followed by a guanine with a phosphate bond, a sequence called cytosine-phosphate-guanine (CpG) island [32]. An increase on methylation of cytosine in CpG islands is associated with a reduced gene transcription [28]. Another process refers to post-translational modifications of histone proteins; whose main mechanism consists of acetylation of lysine residues. This process reduces the affinity between proteins and DNA, promoting a relaxation of the chromatin structure and also increasing the recruitment, activation and stabilization of the transcriptional machinery [37]. The acetylation levels along of the chromatin are determined by the balance between HAT, which adds acetyl groups, and HDAC, which removes acetyl groups from lysine residues in histone [30]. The histone acetylation level is determined by the balance between HAT and HDAC enzyme activity, and thus determines the level of transcription of associated gene [29]. The resilience, a phenomenon of resistance and ability to cope with adversity throughout life can be seriously impaired when individuals are subjected to traumatic events during critical periods for brain developmental programming and can result in long-lasting detrimental consequences throughout life and adulthood [34]. In fact, recent literature has pointed out that epigenetic changes resulting from stress in childhood are inherent in a repertoire of biological processes involved in depression [12,34,58]. In hippocampus of suicide victims, who suffered various forms of abuse and neglect in childhood, studies showed increased methylation of gene promoter region for glucocorticoid receptor (GR) in parallel with a reduction in the GR mRNA levels and GR expression [31,38]. These findings translate results obtained from the hippocampus of rat subjected to maternal deprivation, in which the authors also observed increased depressive-like behavior [67]. Other researchers using MD protocols, also observed increased depressive-like behaviors in parallel with increase of HDAC activity in the rat NAc [48]. It is important to note that the increase in DNA methylation and depressive-like behaviors were reversed with HDAC inhibitors [67]. Indeed, the inactive chromatin is associated with methylated DNA [59], which supports the findings about correlation between inhibition of HDAC and reversing of DNA methylation and depressive behavior. Some studies have shown that classical antidepressants, as well as fast-acting drugs seem to reverse the epigenetic alterations involved in previous stress in childhood, in animals subjected to MD [48].

Atypical antipsychotic, also has epigenetic effects by reducing the methylation of genes in the central nervous system [19,20], and peripherally [23]. The Food and Drug Administration (FDA) approved quetiapine in 1997 for the treatment of schizophrenia [9]. Several studies have demonstrated the efficacy, safety, and tolerability of quetiapine in the treatment of MDD and bipolar disorders [3,56]. Noteworthy is the fact that TRD patients showed antidepressant responses when treated with quetiapine [13]. Moreover, in animals subjected to chronic stress, quetiapine, unlike fluoxetine a classical antidepressant, reversed depressive-like behavior and improved hippocampal neurogenesis [66]. Quetiapine has serotonergic properties as a 5-HT_{1A} partial agonist, potent $\alpha 1$ and $\alpha 2$-adrenoceptors antagonist, as also is an inhibitor of the norepinephrine transporter, through its N-desalkylquetiapine metabolite [50,60]. These aminergic actions are believed to play a role in its antidepressant properties [27] and increase the therapeutic effect of classical antidepressants [10]. Therefore, the study of drugs targeting neuroepigenetic mechanisms could not only provide insights into the understanding of the mechanisms underlying neurobiological causes of the MDD, but should also accelerate the development of novel pharmacological agents which can be most effective in the treatment of MDD. Therefore, this study was aimed to investigate the effects of quetiapine administration on the depressive-like behavior, as well as on biochemical parameters related to DNA methylation and histone acetylation in the adult rat subjected to MD during early life.

2. Experimental procedures

2.1. Animals

Pregnant female Wistar rats (age of 3 months, weight of 250–280 g) were obtained from the breeding colony of Universidade do Extremo Sul Catarinense (UNESC, Criciúma, SC, Brazil) and were housed for one week in the presence of males for sexual experience. At the end of 7 days, pregnant rats (n = 10) were housed individually with *ad libitum* access to food and water. All mothers and pups were kept on a 12 h light/dark cycle (06:00 a.m. to 06:00 p.m.) at a temperature of 23 ± 1 °C, including the pups subjected to MD. Male and female pups were used during the maternal deprivation period, but only half of male were subjected to deprivation, according to the protocol below and schematic drawing (Fig. 1). We take care to select females with approximately the same number of animals, so that the number of animals in the separation of the litter was not much different between them. The whole litter, and the mother rat were housed in a clean box, only after the last day of the MD protocol. After this, the animals were weaned in the 21th postnatal day and housed with five animals per cage. Females were donated to the UNESC vivarium for other studies. Only male rats were used in this research and were primarily divided into two experimental groups: (1) control, non-deprived (n = 23), which received no treatment whatsoever; (2) deprived (n = 21), which were submitted to MD as described. All experimental procedures involving animals were performed in accordance with the NIH Guide for the Care and Use of Laboratory Animals and the Brazilian Society for Neuroscience and Behavior (SBNeC) recommendations for animal care and with approval by local Ethics Committee under protocol number 82/2012.

2.2. Maternal deprivation (MD) protocol

The pups were deprived of the mother for 3 h per day during the first 10 postnatal days (see Fig. 1). In the first postnatal day, the MD protocol was applied to 50% of the male pups during 1–10 postnatal days; other males were used as control. The male pups were randomly selected and after the first withdrawal protocol, deprived pups were marked for the deprivation protocols in the following days. The maternal deprivation protocol consisted of removing the pups from the next box. Non-deprived animals remain undisturbed in a home cage with their mother.

2.3. Drugs and experimental design

Quetiapine (Seroquel®) was provided from AstraZeneca (São Paulo, Brazil). Animals received daily intraperitoneal injections of quetiapine (20 mg/kg) for 14 days. The concentration and treatment period considered a first study published by Ignácio et al. [26] that used quetiapine at the doses of 20, 40 and 80 mg/kg. Lower concentrations of quetiapine elevated the activity of mitochondrial respiratory chain complexes [26]. Furthermore, an unpublished pilot study from our group showed that the concentration of quetiapine at the dose of 80 mg/kg administered acutely revealed a sedative effect, while the concentrations of 20 and 40 mg/kg did not promote sedation, compared to control animals treated with saline. Thus, in the present study we used quetiapine at the dose of 20 mg/kg. Quetiapine was dissolved in saline (0.9%, NaCl) solution (vehicle). Control animals received saline (0.9% NaCl; 1.0 ml/kg). When the Wistar rats non-deprived and deprived