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Effects of maternal L-tryptophan depletion and corticosterone administration on neurobehavioral adjustments in mouse dams and their adolescent and adult daughters

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ABSTRACT

Major depressive disorder (MDD), a pathology characterized by mood and neurovegetative disturbances, depends on a multi-factorial contribution of individual predisposition (e.g., diminished serotonergic transmission) and environmental factors (e.g., neonatal abuse or neglect). Despite its female-biased prevalence, MDD basic research has mainly focused on male rodents. Most of present models of depression are also devalued due to the fact that they typically address only one of the aforementioned pathogenetic factors. In this paper we first describe the basic principles behind mouse model development and evaluation and then articulate that current models of depression are intrinsically devalued due to poor construct and/or external validity. We then report a first attempt to overcome this limitation through the design of a mouse model in which the genetic and the environmental components of early risk factors for depression are mimicked together. Environmental stress is mimicked through the supplementation of corticosterone in the maternal drinking water while biological predisposition is mimicked through maternal access to an L-tryptophan (the serotonin precursor) deficient diet during the first week of lactation. CD1 dams and their offspring exposed to the L-tryptophan deficient diet (T) and to corticosterone (80 mg/l; C) were compared to animal facility reared (AFR) subjects. T and C mice served as intermediate reference groups. Adolescent TC offspring, compared to AFR mice, showed decreased time spent floating in the forced-swim test and increased time spent in the open sectors of an elevated 0-maze. Adult TC offspring showed reduced preference for novelty, decreased breakpoints in the progressive ratio operant procedure and major alterations in central BDNF levels and altered HPA regulation.

The route of administration and the possibility to control the independent variables predisposing to depressive-like symptoms disclose novel avenues towards the development of animal models with increased external and construct validity. Furthermore, the observation that, compared to adult subjects, adolescent mice display an opposite profile suggests that peri-pubertal developmental processes may interact with neonatal predispositions to calibrate the adult abnormal phenotype.

1. Introduction

Major depressive disorder (MDD) affects 2%–5% of the Western countries population in its most severe form and approximately 20% of the population in its milder forms (Weissman et al., 1996; Nestler et al., 2002). Main symptoms of MDD are impaired coping with negative events, reduced ability to experience pleasure from natural rewards (anhedonia), neurovegetative symptoms and thoughts of death or suicide (Bessa et al., 2009). Associated features include altered hypothalamic–pituitary–adrenal (HPA)-axis activity (Krishnan and Nestler, 2008) and neurotrophic factor regulation (e.g., Martinowich et al., 2007). The gender-related issue in the development of animal models for the investigation of depression is often disregarded. A large body of evidence reports that the prevalence of major depression in

Abbreviations: 5-HT, 5-hydroxytryptamine or serotonin; 5-HIAA, 5-hydroxyindoleacetic acid; 5-HTT, serotonin transporter; AFR, animal facility reared; ANOVA, analysis of variance; BDNF, brain derived neurotrophic factor; DRL-72 s, differential reinforcement of low rate 72 s; DSM, diagnostic and statistical manual of mental disorders; ELISA, two-site enzyme-linked immunosorbent assay; FR, fixed ratio; HPA, hypothalamic-pituitary-adrenal; ICD, international statistical classification of diseases and related health problems; KO, knockout; MDD, major depressive disorder; P, postnatal day; PLSD, protected least significant difference; PR, progressive ratio; RIA, radioimmunoassay; SEM, standard error of the mean.

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women is about twice as high as in men (Young et al., 1990; Kornstein, 1997; Maier et al., 1999; Frackiewicz et al., 2000; Nestler et al., 2002). In particular, the female-biased prevalence is particularly elevated in MDD comorbid with anxiety disorders (Breslau et al., 1995). Gender differences in emotional behavior (Gray, 1971; Archer, 1975; Blanchard et al., 1991; Johnson and File, 1991; Perrot-Sinal et al., 2000) as well as sex-dependent differences in neurotransmitter and neuromodulatory systems, particularly the serotonergic system (Carlsson and Carlsson, 1988; Wilson and Biscardi, 1994), have been documented in a variety of mammals. Nevertheless, hardly ever the studies on the relationships between the serotonergic system and neurobehavioral parameters potentially linked to depression and anxiety, involve females (Blanchard et al., 1995; Palanza, 2001).

Clinical and epidemiological evidences indicate that stressful early life experiences, in the form of infant abuse, neglect or parental loss, are associated with increased long-term vulnerability to MDD (Heim and Nemeroff, 1999; Kaufman et al., 2000; Penza et al., 2003; Rutter, 2003; Teicher et al., 2003). Depression has been specifically associated with alterations of serotonin (5-HT) transmission (Owens and Nemeroff, 1994; Baldwin and Rudge, 1995; Porter et al., 2004). Although both aspects have been shown to play a role in the onset of emotional disturbances, depression has been proposed to depend on an interaction between life stress and serotonin dysfunction (Caspi et al., 2003). Specifically, Caspi et al. (2003) have shown that the low-expression variant of a common functional polymorphism in the promoter region of the serotonin transporter gene is associated with increased incidence of major depression in adult individuals experiencing childhood maltreatment or other major life events (e.g., partner's death, major disabilities, and cancer). Several studies thereon attempted to either replicate or further detail the original observations. While some authors failed to replicate the original findings (e.g., Gillespie et al., 2005), other studies reported an association between these polymorphisms and life stressors in the onset of depression (e.g., Conway et al., 2010). The contradictory findings have been generally related to methodological differences in the selection of the study population.

Despite the presence of conflicting data in human studies, experiments performed in laboratory animals support the view that alterations in serotonin transmission and repeated environmental stressors result in behavioral and neurophysiological alterations reminiscent of human depression. Specifically, in rodents, both environmental stress and oral corticosterone exposure result in increased HPA reactivity, behavioral fearfulness and reduced motivation to self-administer palatable rewards (Sheline et al., 1996; Magariños et al., 1998; Rüedi-Bettschen et al., 2005; Gourley et al., 2008a; Leventopoulos et al., 2009). These effects have been observed both when stressors were applied in adulthood and early in development (Macrì and Laviola, 2004; Macrì et al., 2009). Mouse models also support the view of a dysfunctional serotonergic system in the emergence of depressive-like abnormalities (Macrì et al., 2009). Specifically, mutation of the serotonin 1A receptor in 5-HT_{1A} receptor null mice causes increases in anxiety-related behavior (Heisler et al., 1998; Parks et al., 1998; Ramboz et al., 1998; Gross and Hen, 2004). Finally, using a conditional knockout, Gross et al. (2002) blocked serotonin 1A receptor expression between the early embryonic stage and weaning, and thereafter restored normal receptor expression. This group of subjects were confronted with mice in which serotonin receptor expression was blocked in adulthood but not during development. Using this strategy, the authors demonstrated that serotonin receptor blockade resulted in increased anxiety if applied early in development but not during adulthood (Gross et al., 2002). Finally, it is known that non-human primates (rhesus monkeys) with the low-expression variant of the analogous of the aforementioned functional polymorphism have low levels of 5-HIAA (the main metabolite of 5-HT) in the cerebrospinal fluid (Suomi, 2006). A complete review of the depressive-related abnormalities in mice with mutation of serotonergic elements (either constitutive knockout (KO), tissue specific, or inducible KO mice) can be found in the works of Gardier and colleagues (Gardier, 2009; Gardier et al., 2009).

2. Main limitations of current animal models for the investigation of depression

Animal models allow investigating brain-behavior relations, with the aim of gaining insight into normal and abnormal human behaviors and its underlying neuronal and neuroendocrine processes (van der Staay, 2006). Specifically, animal models for the investigation of depression are used to study the etiological factors involved in this pathology and are aimed at developing novel therapeutic strategies (Bessa et al., 2009). However, current mouse models attempting to mimic human depression suffer from limited validity at several levels (Willner, 1991). Indeed, in the development of an animal model of behavioral dysfunction the concept of validity is of primary importance (van der Staay, 2006). According to a set of criteria proposed by McKinney and Bunney (1969), a model should resemble the condition it models in its etiology, biochemistry, symptomatology and treatment (van der Staay, 2006; van der Staay et al., 2009 for a comprehensive description of validity criteria).

With respect to construct validity neither stressful life events nor serotonin transmission dysfunction *per se* is sufficient to induce a major depressive phenotype (Tanke et al., 2008). A reconsideration of the multifactorial aetiology of MDD and new methodological approaches strongly suggests that risk for depression is determined by a combination of genetic and environmental factors (Lesch, 2004), such as stressful life events and particularly adverse early experiences (Chapman et al., 2004; Lazary et al., 2008). As discussed above, most of present animal models for the investigation of depression have limited efficacy partly due to the fact that they only address the biological (genetic preparations) or the environmental mediators of depression (maternal separations and/or early stress, Macrì and Würbel, 2006) thereby holding limited construct validity (they fail to mimic the pathology in its aetiology). Such poor construct validity increases the number of false positive and false negative findings in basic research, thereby limiting the possibility to develop novel therapeutic strategies. This, in turn, hampers the possibility to translate basic research into clinical practice. Until now only a small number of studies have tried to model the gene × environment interaction in the induction of depressive-like phenotypes in rodents (e.g., Carola et al., 2006). Recently, Carola et al. (2008) developed such paradigm in the mouse testing interactions between heterozygous null mutation in serotonin transporter (5-HTT) and rearing environment (spontaneous level of maternal care) on anxiety and depression related behavior.

External validity, the possibility to extrapolate the findings obtained within a given experimental context (e.g., strain, species, laboratory, and time of the year) to other situations, is also largely neglected both theoretically and empirically. Current genetic preparations generally apply to a given background mouse strain, thereby eliminating the possibility to replicate a given finding in different strains (both inbred and outbred). Recently, such logic has been criticized whereby confining all mutant studies to one specific background may lead researchers to miss interesting and relevant phenotypes (Richter et al., 2009).

3. An experimental approach aimed at overcoming the aforementioned limitations

To overcome the aforementioned limitations, we developed a refined mouse model for the investigation of depression combining its biological and environmental etiological factors. Additionally, we aimed at proposing a mouse model applicable to different mouse strains. Construct validity-wise we combined an early environmental