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Multifaceted strain-specific effects in a mouse model of depression and of antidepressant reversal

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Summary Etiopathogenesis of depression and the cause of insensitivity to treatment remain poorly understood, although genetic makeup has been established as a contributing factor. The isogenicity of inbred mouse strains provides a useful tool for investigating the link between genes and behavior or drug response. Hence, our aim was to identify inbred mouse strains (among A/J, BALB/c, C3H, C57BL/6, CBA, DBA and FVB) sensitive to a 9-week period of unpredictable chronic mild stress (UCMS) and, from the fifth week onward, to the reversal effect of an antidepressant (AD) (imipramine, 20 mg/kg/day i.p.) on various depression-related changes: physical, behavioral and neuroendocrine states. UCMS induced a significant deterioration of the coat state (in all the strains), blunted emotional reactivity in the novelty-suppressed feeding (NSF) test (A/J, BALB/c, C57BL/6), and changes in the level of fecal corticosterone metabolites (BALB/c, C57BL/6, DBA, FVB). Imipramine treatment reversed the UCMS-induced alterations of the coat state (BALB/c, DBA), in the NSF test (A/J, BALB/c, C57BL/6) and in fecal corticosterone metabolites (BALB/c, C57BL/6). C3H, CBA and FVB mice were irresponsive to imipramine treatment. It is noteworthy that UCMS-induced physical or behavioral changes occurred without hypothalamo—pituitary—adrenal (HPA) axis alterations in some strains (A/J, C3H, CBA), although the AD-induced reversal of these changes in BALB/c and C57BL/6 was associated with HPA axis normalization. Finally, UCMS is shown to discriminate various alterations and to replicate in a strain-dependent manner diverse profiles reminiscent of human disease subtypes. UCMS may thus enable the selection of strains suitable for investigating specific depression-related features and could be an appropriate model for identifying genetic factors associated with increased vulnerability, specific symptoms of affective disorders, and AD resistance.

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1. Introduction

Major depressive disorder (MDD) is one of the most common and serious health problems of western societies (Murray and Lopez, 1997). MDD is not a well-defined syndrome as it encompasses various subtypes with different patterns of symptoms. While the etiology of MDD is multifactorial and far from perfectly understood, chronic stress or stressful events have been identified among the major environmental factors precipitating depression (Kendler et al., 1999; Riso et al., 2002; Hammen, 2005). This is corroborated by the frequent occurrence of neuroendocrine stress system disturbances in MDD, such as hypercortisolemia and negative feedback impairments of the hypothalamo–pituitary–adrenal (HPA) axis (Arborelius et al., 1999; Holsboer, 2000; Gold and Chrousos, 2002; Barden, 2004). However, an adverse experience does not automatically trigger depressive episodes, but vulnerability is related to the individual's history of stressful life events as well as developmental, genetic and epigenetic factors (Caspi et al., 2003; Craddock and Forty, 2006; Goldberg, 2006; Mill and Petronis, 2007). Likewise, the heterogeneous pattern of symptoms, the presence of HPA disturbances and the frequently observed insensitivity to antidepressants (AD) could stem from the genetic makeup. Knowledge of the genetic basis of these individual differences could help to unravel the source of vulnerability, MDD subtypes and AD resistance. Animal models can be useful to facilitate the discovery of candidate genes.

Studies on inbred mouse strains can provide a powerful tool for understanding the influence of genes in normal and disordered brain function. Interestingly, variability in the response of different inbred mouse strains has been observed in various paradigms such as the forced swimming test (FST) (Bai et al., 2001; Lucki et al., 2001; David et al., 2003), the tail suspension test (TST) (Bai et al., 2001; Liu and Gershenfeld, 2001; Ripoll et al., 2003; Crowley et al., 2005; Liu et al., 2007) or the unpredictable chronic mild stress (UCMS) (Pothion et al., 2004; Ducottet and Belzung, 2005; Mineur et al., 2006). However, sorting strains according to their propensity to develop depression-like behaviors or AD response would appear to be vain in view of the discrepant results of studies. This discrepancy could be due to the diversity of paradigms used. Their common feature is sensitivity to ADs, but they differ in the theoretical background with which they are constructed. The most widely used paradigms are the FST and the TST. Both tests are based on exposure to a single aversive and inescapable situation which induces a behavioral shift from struggling to immobility. A single AD administration can decrease the duration of immobility (Porsolt et al., 1977; Steru et al., 1985; Cryan and Holmes, 2005). The utilization of these tests for AD drug detection gained popularity as pharmacological screening assays, but have been increasingly used for studying neurobiology and pathophysiology as well as for identifying genes causing depression. However, the fact that MDD is a chronic disease and that ADs are only clinically active after a minimum of three weeks treatment makes the validity of such paradigms questionable, particularly when examining the mechanisms involved in the etiology, maintenance and treatment of MDD. Chronic models of depression, such as the UCMS paradigm, could provide an alternative method, avoiding such drawbacks. UCMS is based on subjecting mice to a period (generally five to nine weeks) of mild socio-environmental stressors. This procedure replicates several depression-related behavioral and physiological impairments which can be reversed by chronic, but not acute, AD treatment (Belzung and Surget, 2008): decreased sucrose consumption (interpreted as anhedonia), increased fearfulness/anxiety-related behaviors, altered weight gain, deterioration of the coat (interpreted as the loss of interest in performing customary tasks).

A survey of inbred mouse strains in the UCMS paradigm could be a step toward identifying genes involved in vulnerability to stress exposure, the development of different MDD-associated symptoms, and insensitivity to AD. The major goal of the present study was to identify inbred mouse strains sensitive to the UCMS procedure and in which ADs can reverse various depression-related changes. Mice from seven different strains (A/J, BALB/c, C3H, C57BL/6, CBA, DBA and FVB) were subjected to a 9-week UCMS regimen. From the fifth week onward, vehicle or imipramine (20 mg/kg) was administered i.p. daily. The effects of UCMS and of imipramine treatment were assessed using physical measures (coat state, weight), behavioral tests (novelty-suppressed feeding [NSF] test and actimeter), and the level of fecal corticosterone metabolites was measured to assess HPA axis functioning.

2. Methods

2.1. Animals

Male mice from seven inbred strains (A/J, BALB/cByJ, CBA/J, C3H/HeJ, C57BL/6J, DBA/2J, FVB/NJ) were obtained from the Centre d'élevage Janvier (Le Genest Saint Isle, France) and Harlan (Gannat, France). They were aged seven weeks on arrival in our lab. Before the onset of the experiments, all animals were housed in groups of 5 and were maintained under standard laboratory conditions with a 12/12 h light/dark cycle (lights on at 20:00 h), 22 ± 2 °C, food and water *ad libitum*. The treatment of the animals complied with the European Community Council directive 86/609/EEC.

2.2. Drugs

Imipramine hydrochloride (Sigma–Aldrich) was used in this study. Imipramine was prepared as solutions in physiological saline (NaCl 0.9%). Concentration was adjusted to administer a final volume of 10 ml/kg.

2.3. General procedure

On arrival, mice were kept in the laboratory for two weeks before the onset of the experiments. A 9-week UCMS procedure was then conducted. UCMS-exposed mice (2/3) were maintained under standard laboratory conditions but were isolated in small individual cages (24 cm × 11 cm × 12 cm), while non-stressed control mice (1/3) were housed in groups of 4 or 5 in standard laboratory cages (42 cm × 28 cm × 18 cm). The first four weeks of the UCMS regimen were drug-free, and treatment began from the fifth week of UCMS and continued to the end of behavioral testing. Vehicle (0.9% NaCl) or imipramine (20 mg/kg/day) was administered i.p. once a day. The dose was chosen on the basis of previous experiments showing