Measuring behavior with chronic stress depression models in mice

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Chronic stress is regarded as one of the most adequate methods for mimicking depression in rodents, because it 1) fits the face validity criteria by implication of induction of anhedonia, a core symptom of depression, and 2) simulates etiological relevance of stress with this disorder [1, 2]. At the same time, studies, using chronic stress depression models, failed to define a consistent behavioral phenotype of a depressive-like state seen in chronically stressed rodents and overall, resulted in abstruse and variable outcome [3]. This greatly limits a value of this method in modeling depression and decreases its utility for the identification of new mechanisms / targets of antidepressant therapies. Studies with our stress-induced anhedonia model suggest that unresolved methodological difficulties in measuring behavior in chronically stressed animals may underlie these problems.

Lack of a proper control

Perhaps the most obvious problem with measuring behavior during stress-induced anhedonia consists in the shortcoming that all effects observed in groups of stressed animals are attributed to a depressive-like syndrome and anhedonic state. Meanwhile, stress *per se* can evoke a number of physiological alterations, which are not associated with depression. Since available chronic stress models did not provide a control for the effects of chronic stress alone, strictly speaking, it was not possible to relay findings obtained in chronically stressed animals selectively to a depressive-like phenotype and hedonic deficit. We established an anhedonia-evoking stress regimen, upon which not all individuals, but only about 50-70% of C57BL mice, develop a hedonic deficit [4]. Employment of the stressed non-anhedonic group as an internal control for the effects of chronic stress *per se* enabled the first attempt to separate behavioral features of anhedonia and consequences of chronic stress alone. We found that anhedonia is selectively associated with depressive-like behaviors, such as "behavioral despair" in the forced swim and tail suspension tests and decreased novelty exploration; these deficits were not observed in non-anhedonic animals. Increased anxiety and changes in locomotion were detected in stressed mice with and without hedonic deficit. Studies with a model of social defeat stress on the C57BL6 strain confirm our data on percentage of individuals resilient /susceptible to a development of stress-induced depressive-like state and on their behavioral differences [5].

Low resolution of sucrose test

Decreased intake of palatable solutions, e.g., of sucrose, is taken as a behavioral measure of hedonic deficit / depressive-like state [1]. Insufficient accuracy of the sucrose test in mice is another key difficulty in measuring behavior with chronic stress depression models. Typically, sucrose test can let to reveal the differences between the groups, but not between the individual mice. We showed that side preference, neophobia, individual differences in circadian patterns of liquid intake, experience of sucrose taste and other factors, when not taken under control, result in physiological and physical artifacts in evaluating sucrose drinking behavior [6]. Modification of this test that included switching the choice bottles during testing, allowed us to increase its resolution and assess the hedonic state of mice on an individual basis.

Behavioral artifacts resulted from a stress-induced hyperlocomotion

The majority of studies with chronic stress depression models demonstrated paradoxical and inconsistent behavioral changes [1,3]. Our studies in mice identified a phenomenon of hyperlocomotion, an unspecific consequence of chronic stress, which is triggered by a stressful procedure of testing [6,7]. Reduction of the stress impact of testing conditions, e.g., diminishing light intensity, precluded artifacts caused by this phenomenon and let us to determine consistent behavioral phenotype of chronically stressed mice using a variety of tests.

Social behavior as a source of behavioral variability

Even though we used genetically homogeneous mice, we observed pronounced individual variability in animals' susceptibility to stress-induced anhedonia, which was predicted by subdominant social traits. Stress-induced changes in parameters of sucrose test and other behaviors were depending on percentage of aggressive and non-aggressive individuals in a stressed population, evaluated in baseline conditions [7]. Variability of mouse populations in social behavior presumably underlies significant diversity in behavioral stress response of mice from different batches; in order to ensure a proper stress load, characteristics of stressors had to be adjusted to behavioral parameters of a tested population.

Together, we believe that the findings obtained in our paradigm of stress-induced anhedonia can help to explain and overcome some of the major difficulties in measuring behavior with chronic stress depression models.

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