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Review

Animal models of extinction-induced depression: Loss of reward and its consequences

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ABSTRACT

The absence or loss of rewards or reinforcers holds a major role in the development of depression in humans. In spite of the prevalence of extinction-induced depression (EID) in humans, few attempts have been made to establish animal models thereof. Here we present the concept of extinction-related depression and summarize the results of two sets of studies in our attempt to create animal models of EID, one set based on extinction after positive reinforcement in the Skinner-box, the other on extinction after negative reinforcement - escape from water. We found various behaviors emitted during the extinction trials that responded to treatment with antidepressant drugs: Accordingly, the important behavioral marker for EID during extinction of escape from the water was *immobility*. During extinction after positive reinforcement the important indices for extinction-induced depression are the *withdrawal* from the former site of reward, *biting behavior* and *rearing up* on the hind legs. Avoidance behavior and biting may model aspects of human depressive behavior, which may include withdrawal or avoidance as well as aggressive-like behaviors.

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1. Introduction

There is obviously a dire need for new behavioral animal models of depression, as a new plea for such appears on a regular basis in innumerable publications (Anisman and Matheson, 2005; Berton et al., 2012; Edwards and Koob, 2012; Nestler and Hyman, 2010). While considerable effort is being devoted to genetic and

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molecular models of mental disease (Krishnan and Nestler, 2011; Nestler and Hyman, 2010), there has been little progress in the development of behavioral models as operational definitions of the symptoms of the disease, without which molecular animal models are of questionable relevance, since these are dependent on behavioral readout to validate them as being related to depression. In this respect, we seem to have the blind leading the blind in-so-far as there is wide skepticism as to the criteria of validity of the most widely used behavioral screening devices for depressive behavior in rodents. High throughput screening of drugs demands simple, easy to use behavioral assays, as do non-behaviorally oriented scientists, who lack the training or means to perform complicated behavioral tests, which precludes the use of certain models that may have appeal in terms of face- and construct validity (like the learned helplessness paradigms, conditioned suppression, etc.; Krishnan and Nestler, 2011). As much has been said about the dearth of relevant models and the limitations of the available ones (Belzung and Lemoine, 2011; Cryan et al., 2002; Duman, 2010; Fernando and Robbins, 2011; Nestler and Hyman, 2010; Nestler et al., 2002; Pollak et al., 2010; Willner and Mitchell, 2002; Geyer and Markou, 2002), we will not pursue this issue here. Instead, we will present a new behavioral model of depression that shows promise in rats and may prove useful also in other animal species, including primates.

We include the essay in this commemorative special issue for Ann Kelley and see our work in the context of her devotion to exploring the neurobiological mechanisms that control the motivational systems related to operant conditioning, addiction processes, incentive action and, particularly relevant for our model here, the extinction of operant behavior (Andrzejewski et al., 2011).

1.1. Subtypes of depression

It is well known that the depressive syndrome is not a unitary phenomenon with a unitary etiology. Instead, the term "depression" encompasses a heterogeneous class of problems and depressive behaviors with many causal factors, including inherited and experiential ones that may interact (genetic susceptibility, epigenetic variation, concurrent disabling diseases, substance abuse, chronic and acute environmental triggers, stress-related coping mechanisms) and so could the underlying biochemical and neural mechanisms that are dysfunctional and that should be targeted by pharmacological or behavioral therapies. Although the Diagnostic and Statistical Manual of Mental Disorders (DSM IV, American Psychological Association, 2000) differentiates between depression resulting from substance abuse, brain damage or related to a medical factor, the diagnosis of a major depression is simply based on the occurrence of a specified number of symptoms without taking into account different causes. Is depression that evolves from chronic stress identical to that which accompanies psychiatric and neurological disorders or to that which is triggered by acute aversive events and trauma or to seasonally appearing depression? Is depression in the aged the same as in youths and adults? Are there major gender differences? Can a few simple animal models model all of these variants? Can a few classes of drugs be expected to optimally treat all of the variants of depression? Can all subtypes really be subsumed by a few concepts such as "stress" and "learned helplessness" and the related behavioral models? Or should we attempt to construct animal models for a variety of subtypes and categories of depression? We favor the latter approach and in this review present several variants of a behavioral rodent model of a subtype, namely, extinction-induced depression (EID).

2. Loss of reward and its consequences

A powerful source of success, joy and well being in humans is the attainment of reward/reinforcers. Most organisms exhibit behavioral flexibility mainly in the service of attaining biologically critical sources of nourishment, shelter, safety and procreation. These needed or wanted events or goals are termed primary "reinforcers" or "rewards" in so far as they can serve to attract the organism and, most importantly, to have the property of modifying or shaping the organism's behaviors contingent on their attainment. It is obvious that the absence or failure to obtain biologically crucial rewards can have dire consequences for survival. It follows that the absence or scarcity of such rewards can also have powerful emotional and behavioral consequences. Usually, higher organisms "learn" behavior patterns that will maximize the attainment of rewarding events. A century of animal experimentation has established the power of rewards to establish and maintain a vast variety of behaviors and such control by rewarding events over behavior has been subsumed by the concepts of operant or instrumental conditioning. Once the relationship between a specific behavior or behavioral pattern and retrieving reward afterwards is established, the organism can be said to anticipate the reward/reinforcer (without necessarily implying an awareness of a behavior/reward contingency). When such an "expected" reward ceases to appear, the organism learns that the formerly adaptive response is no longer effective in leading to the reward and will gradually cease to emit it and the "intelligent" organism will engage in alternative behaviors or seek alternative sources of reward. The behavior that was formerly successful in predicting the rewarding event is said to undergo "extinction" as a consequence of the non-availability of the reward. It makes sense that such an event will not only have consequences for the organism's behavior, but also powerful negative emotional effects subsumable with constructs such as "anxiety", "despair", "anguish", "frustration", "stress" and ultimately "depression". We will designate depression-like behavior resulting from loss of reward as "extinction-induced depression" (EID).

3. Extinction-induced depression (EID)

We can loosely differentiate between three major categories of environmental events that can be causes of despair and depression:

1 Uncontrollable aversive, punishing events.
The absence of potential reinforcers/rewards.
The withdrawal of reinforcers/rewards, which results in the extinction of instrumental (operant conditioned) behavior.

There are a number of well known available animal models for the first category, including the forced swim test (Porsolt et al., 1977), tail suspension (Cryan et al., 2005), the learned helplessness paradigms (Seligman, 1972), and the chronic mild stress model (Willner, 2005; Willner et al., 1992). For the second category, ethical constraints may prevent studying such effects. However, studies have examined the effects of social and maternal deprivation, which represent the absence of potential reinforcers early in life (for review see: Gilmer and McKinney, 2003; Newport et al., 2002). Various animal models of social and maternal deprivation are also available (Fone and Porkess, 2008; Hall, 1998; Marco et al., 2009; Matsumoto et al., 2005). We will focus here on the third category and present variations of the recently developed animal models.

3.1. The EID hypothesis

The absence of a reinforcer (in the case of a foraging organism), or the withholding of a reinforcer (in the case of a learned

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