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COMMENTARY

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What is mild in mild stress?

The attempt to evaluate validity, reliability and utility of the chronic mild stress (CMS) model of depression after more than a decade of use in preclinical studies is certainly useful. This model is based on a labour intensive, space demanding and long stress procedure which consists of exposing animals sequentially to a variety of "stressors" for a period of weeks. Stress-based animal models represent an indispensable preclinical approach to human pathology, since clinical data point to a major role stress experiences ("life events") in the development, expression and exacerbation of behavioral disturbances (Gottesman and Shield 1982; Willner 1991; Fowels 1992; Anisman et al. 1993; Cabib and Puglisi-Allegra 1996; for review). Thus, the stress procedure is one of the major strengths of the CMS model and it is surprising that most of Willner's review is dedicated to supporting the model as "simulation" of symptoms of the melancholic subtype of endogenous depression, whilst little, if any, space is given to the evaluation of CMS as a model of pathogenic "life events".

The most strongly emphasized feature of CMS procedure is the use of "mildly stressful" experiences aimed at reducing the level of imposed stress to the bare minimum (Muscat and Willner 1992) and at representing a realistic simulation of the etiology of depression involving "...chronic low grade stress" (Willner et al. 1992). The experiences used are considered mildly stressful according to the UK legislation [The Animals (Scientific Procedures) Act 1986]. However, the grade or intensity of stress is extremely difficult to evaluate and it involves a high risk of error, especially when different species are considered. Thus, as an example, individual housing may represent a stressful condition for highly social species or for developing organisms, but it might be seen as an optimal housing condition for adult males of territorial species (Brain 1975).

The intensity of experimental stress may be evaluated by its effects. The effects promoted by the CMS procedure are those observable following a single experience with so-called severe stressors (Cabib and Puglisi-Allegra 1996, for review). Moreover, CMS produces a sort of sensitisation to the behaviourally impairing effects of stressors (Muscat and Willner 1992), whilst repeated exposure to the same, even severe, stress promotes habituation/adaptation to the stressor (Cabib and Puglisi-Allegra 1996). Consequently, CMS is the only chronic procedure capable of promoting the effects of a severe stressor.

Moreover, independent studies using different species (rats and mice) and different measures of the anhedonic effects have demonstrated that none of the individual "stressors" is either necessary or sufficient, whilst variability and repetition of experiences are indispensable for the effectiveness of this procedure (Griffiths et al. 1992; Muscat and Willner 1992). In other words, what is stressful in CMS is the repeated exposure to variable experiences rather than the experiences in themselves. The ability of CMS to promote the effects of severe stress regardless of the specific experiences to which the animals are sequentially exposed is relevant, since it supports the view that the stressful characteristics of experimental manipulations do not depend on their physical impact.

Indeed, a number of researches, starting from the early work by Mason (1975), have consistently demonstrated that the behavioural and physiological disturbances related to stress are not dependent on the intensity of the noxious stimulation, but on specific psychological parameters such as novelty, uncontrollability, uncertainty and unpredictability (Seligman 1975; Weinberg and Levine 1980; Weiss et al. 1981; Cabanac 1990; Wiepkema 1990; Anisman et al. 1993; Huether 1996). In this view, variability and unpredictability of the experiences to which the animals are sequentially exposed prevents the development of coping strategies (control) or habituation (Cabib and Puglisi-Allegra 1996, for review) thus producing a chronic condition of novelty, uncertainty and helplessness.

Consequently, CMS cannot be considered a mild stress procedure either for its effects or for its modalities. Since the necessity to use mild stress in an animal model

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of depression is motivated by ethical and methodological reasons (Muscat and Willner 1992; Willner et al. 1992), it is worth making a few observations in this regard. The notion that depressive symptoms may arise from "low grade" stress may be well explained by the polygenic model of psychopathology. According to this model, pathological outcomes derive from the interaction between environmental (stress) and individual (genetic and/or experiential) factors. The relationship between individual and environmental liability may be viewed on a continuum with an upper extreme of highly susceptible individuals who develop pathology regardless of the environmental contribution, a lower extreme of individuals resistant also to severe environmental challenges and a large, intermediate segment in which the severity of environmental pressure may be regarded as the major determinant of liability (Fowels 1992).

The ability of severe negative experiences to induce depression is widely recognised and well documented by epidemiological studies (see Fowels 1992; for review). Moreover, these studies indicate that severe life events can produce the syndrome of depression in individuals with no detectable prior vulnerability, confirming that stress is a potent contributor to depression. On the other hand, individual factors contribute to the severity of environmental pressure since they may exacerbate the impact of "low grade stress" and even render "positive" changes in everyday life intolerable experiences. Indeed, marriage may be listed amongst pathogenic life events (Holmes and Rahe 1967). Thus, in animal models, pathogenic effects of low grade stress may only be simulated in a restricted population of subjects vulnerable to otherwise ineffective stressors due to their genetic constitution or acquired susceptibility. Instead, in the absence of such vulnerability, only severe stress conditions are expected to represent the "bare minimum" capable of simulating pathological disturbances reliably. Finally, since depression involves the whole continuum of liability, preclinical research cannot limit its approach to one extreme sample if it intends to produce meaningful information for clinical intervention.

The latter observation leads us to evaluate another aspect of CMS procedure that is emphasized in the present review: its ability to promote symptoms of the melancholic subtype of major depression "selectively". In this line, all reported effects of CMS are possible models of the various symptoms of this pathology. Moreover, CMS is reported not to cause the appearance of an "anxious" profile, which indicates that behavioral disturbances promoted by this procedure are not only specific to depression but also to specific subtypes not involving symptoms of anxiety. However, CMS promotes a wide spectrum of disturbances (Cabib and Puglisi-Allegra 1996, for review) and other experimental stress procedures have been shown to reduce sensitivity to rewards, the core symptom of melancholic depression, reliably (Zacharko and Anisman 1991).

The demonstration that stress-promoted disturbances are not specific to a single symptomatic profile is a strength rather than a weakness for an animal model. Indeed, the possibility that stress-induced disturbances are stressor-specific (i.e. if there exists a psychosis-eliciting stressor, a stressful condition that promotes a dysthymic symptomatology selectively and so-on) has been generally rejected both at clinical (Rosenthal 1970; Gottesman and Shield 1982; Fowels 1992) and preclinical (Zacharko and Anisman 1991; Cabib and Puglisi-Allegra 1996; Puglisi-Allegra and Cabib 1997) level. Thus, if an experimental stress promotes specific disturbances, these might be considered part of a specific syndrome of stress maladaptation (Lechin et al. 1996) quite distinct from depression or from other psychopathologies.

Finally it should be pointed out that if environmental factors are not specific for a given pathology, the genetic factors are (Rosenthal 1970; Fowels 1992). Thus, the strain- and supplier-dependent susceptibility to CMS-induced anhedonia discussed by Paul Willner in the present review should be further investigated since it might indicate differential individual susceptibility to the different alterations promoted by the stressful condition. In other terms, strains of rats which are resistant to development of experimental anhedonia under the CMS paradigm could develop other types of disturbances. In this sense, the repeated variable stress paradigm appears to be a promising model that is yet to be exploited.

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