

## **SIMULATING DEPRESSION IN ANIMALS: STRESS-INDUCED ANHEDONIA AS A CASE STUDY**

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Anhedonia, the loss of interest or pleasure in daily activities, is a core symptom of depression. A similar state of decreased capacity to experience pleasure can be reproducibly induced in rats by a regimen of chronic, mild, unpredictable stressors (CMS) (Willner, 1997). This CMS procedure elicits a number of behavioral and physiological abnormalities (e.g. decreased sexual and exploratory behaviors, sleep abnormalities, dysregulated immune and HPA axis activities) which are reminiscent of symptoms of depression. The hedonic state of animals submitted to such a chronic stress regimen was originally assessed through measurement of sucrose consumption/preference. The construct validity of this model rested on the assumptions that 1) CMS caused a generalized decrease in reward sensitivity, and 2) sucrose drinking was a valid measure of sensitivity to reward. The first assumption seems to be verified in that CMS has now been shown to induce hedonic deficits measurable in a variety of behavioral paradigms. However, the second assumption raises problems with respect to reliability and/or interpretation of the results. Indeed, stress-induced decrease in sucrose consumption/preference varies between experiments, with animal strain used, and according to particular stress procedures. Other confounding factors, such as loss of body weight resulting from food deprivation being part of the stress procedure, were said to be sufficient to produce sucrose consumption deficits. These variations indicate that this paradigm is not the most appropriate technique reliably and unambiguously to measure stress effects on motivated behaviors. We had therefore to consider alternative behavioral endpoints as indices of hedonic responsiveness.

One of the most recognized and most appropriate behavioral paradigms to measure sensitivity to reward is intracranial self-stimulation (ICSS) behavior. This technique offers direct activation of brain substrates involved in these hedonic

processes (such as the ventral tegmental area). Self-stimulation threshold can thus be used as valid index of the hedonic state of an animal (Markou & Koob, 1991). An additional advantage of the ICSS technique is that brain stimulation reward can be readily varied in intensity (as opposed to food reward), allowing determination of individual sensitivity to reward in a much more precise manner. ICSS thresholds are determined prior to, during and after an extended period of exposure to a variety of stressors. In stressed animals, ICSS threshold progressively increases over a 10-day to 2-week period, indicating a gradual decrease in sensitivity to reward. This anhedonic state lasts throughout the stress regimen. This animal model of depression has been extensively investigated (see table 1) over the past few years (for review, see Moreau, 1998). It offers a fair predictive validity (Papp et al., 1996) as active treatments include representatives of clinically effective antidepressants such as tricyclics, atypical antidepressants, SSRIs, MAO inhibitors, and electroconvulsive therapy. On the other hand, expected ineffective treatments include well-established anxiolytics, antipsychotics, and analgesics. As shown in table 1, this model also offers a number of other interesting features, as it addresses a core symptom of depression (anhedonia), is vulnerable to the same kind of risk factors, and exhibits similar sleep abnormalities (Moreau et al., 1995). It thus qualifies as a validated model of some aspects of human depression. It can therefore be confidently used for both characterizing novel drugs and investigating novel mechanisms potentially involved in the generation of depressive episodes.

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Papp, M., Moryl, E. & Willner, P. (1996) Pharmacological validation of the chronic mild stress model of depression. *Psychopharmacology* 296: 129-136.

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Table 1: Similarities between aspects of human depression and stress-induced anhedonia in rats

	DEPRESSION IN MAN	ANHEDONIA IN RATS
SYMPTOMS	<ul style="list-style-type: none"> <li>. depressed mood</li> <li>. loss of interest or pleasure</li> <li>. decreased sexual drive</li> <li>. low self-esteem</li> </ul>	<ul style="list-style-type: none"> <li>. cannot be simulated</li> <li>. reduced sensitivity to reward (anhedonia)</li> <li>. decreased sexual activity</li> <li>. decreased aggressive behavior</li> </ul>
RISK FACTORS	<ul style="list-style-type: none"> <li>. stressful life events</li> <li>. social isolation in childhood</li> </ul>	<ul style="list-style-type: none"> <li>. chronic mild stress</li> <li>. isolation-reared animals are more vulnerable to chronic mild stress</li> </ul>
BIOLOGICAL MARKERS	<ul style="list-style-type: none"> <li>. sleep abnormalities               <ul style="list-style-type: none"> <li>- decreased REM sleep latency</li> <li>- increased total REM sleep</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>. sleep abnormalities               <ul style="list-style-type: none"> <li>- decreased REM sleep latency</li> <li>- increased total REM sleep</li> </ul> </li> </ul>
ACTIVE TREATMENTS	<ul style="list-style-type: none"> <li>. tricyclics</li> <li>. atypicals</li> <li>. SSRIs</li> <li>. SNRIs</li> <li>. MAO inhibitors</li> <li>. electroconvulsive therapy</li> <li>. others</li> </ul>	<ul style="list-style-type: none"> <li>. amitriptyline, imipramine, desipramine</li> <li>. maprotiline, mianserin</li> <li>. fluoxetine, sertraline, S-citalopram</li> <li>. Venlafaxine</li> <li>. moclobemide, brofaromine</li> <li>. electroshock treatment</li> <li>. Tolcapone, Ketoconazole, NK1 antagonist</li> </ul>
INEFFECTIVE TREATMENTS	<ul style="list-style-type: none"> <li>. anxiolytics</li> <li>. antipsychotics</li> <li>. psychostimulants</li> <li>. analgesics</li> </ul>	<ul style="list-style-type: none"> <li>. chlordiazepoxide</li> <li>. haloperidol, risperidone, chlorprothixene</li> <li>. amphetamine</li> <li>. morphine</li> </ul>