Simulating the anhedonia symptom of depression in animals

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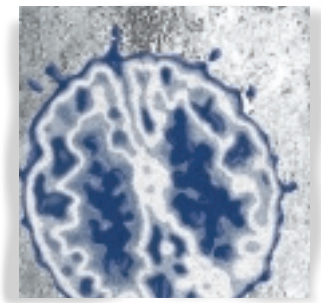

One of the two core symptoms of depression is anhedonia, the loss of interest or pleasure in daily activities. Stressful life events are recognized as predisposing factors in the etiology of depression. Rats subjected to a chronic, mild, unpredictable stress regimen exhibit behavioral deficits consistent with a loss of responsiveness to reward, such as decreased sucrose consumption, decreased ability to associate rewards with a distinctive environment, and decreased sensitivity to rewarding electrical brain stimulation. Normal behavior is restored by chronic treatment with antidepressants or electroshocks. Chronically stressed animals also exhibit sleep abnormalities resembling those observed in depressed patients and recognized as biological markers of depression. Thus, stress-induced anhedonia in rats represents an original animal model of some aspects of human depression offering convergent elements of biological, symptomatological, etiological, and therapeutic validity. This simulation of depression may prove useful for better understanding of the pathophysiological mechanisms involved in depressive disorders.

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Animal models are defined as experimental preparations developed in one species in order to study phenomena existing in another species. When addressing animal models of human psychopathology, attempts are made to reproduce in animals some syndromes or symptoms resembling as far as possible some human syndromes or symptoms in order to study particular aspects of human psychopathology. When utilizing an animal model for studying a human disease, it is important to consider the validity of such a simulation. The validity of animal models of psychiatric disorders is usually assessed by different criteria: ideally, the model should resemble the pathology it simulates in terms of its etiology, its biology, its symptomatology, and its treatment.[1] Three different types of validity are usually considered: predictive validity, aspect validity, and theoretical validity.

Predictive validity is determined by appropriate response of the animal model to therapeutic agents. The model must discriminate clinically efficacious agents from those which are not. The simulation should identify substances that ameliorate, but also those that deteriorate the simulated pathology. In addition, the model must be responsive to all categories of medications used to treat the simulated condition.

Aspect validity refers to phenomenological similarity between the model and the pathology being simulated. It mainly relates to symptomatology and mode of treatment. Usually, models focus on one particular symptom of a given disorder. The difficulty is to appreciate the importance of this particular symptom in the definition of the syndrome. Concerning the treatment, most psychotropic drugs need to be regularly administered over several weeks or months. Consequently, in the model, substances should continue to be efficacious after chronic administration. In addition, and similar to what happens in the clinic, we might expect a delay in the appearance of the first beneficial effects.

Finally, evaluating the *theoretical validity* of an animal model consists in identifying the behavioral variable that will be simulated, estimating its degree of homology with the behavior in the simulation, and appreciating the mean-

ing of this variable in the context of the clinical situation. Here, following a brief description of the symptomatology and etiology of depression, we shall try to demonstrate how to induce and how to measure an anhedonic state in the laboratory rat. We shall summarize the main experiments performed to validate this animal model of depression by reviewing results from behavioral, pharmacological, and electroencephalographic studies.

Symptomatology of depression

Depression is a very complex psychological disorder. Many different symptoms can be present, but none by itself is essential. An episode of major depression is defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*[2] as follows: Five (or more) of the following symptoms have been present during the same 2-week period; at least one of the symptoms is either depressed mood (1) or loss of interest or pleasure (2).

- (1) Depressed mood.
- (2) Markedly diminished interest or pleasure in daily activities.
- (3) Significant weight loss or weight gain (more than 5% of body weight in a month), or decrease or increase in appetite.
- (4) Insomnia or hypersomnia nearly every day.
- (5) Psychomotor agitation or retardation nearly every day.
- (6) Fatigue or loss of energy nearly every day.
- (7) Feelings of worthlessness or excessive or inappropriate guilt.
- (8) Diminished ability to think or concentrate nearly every day.
- (9) Recurrent thoughts of death, recurrent suicidal ideation.

Among all these symptoms of depression, some can easily be modeled in animals (body weight change, psychomotor retardation), whereas others cannot (feelings of worthlessness or guilt, suicidal ideation). *DSM-IV* defines two major symptoms for the diagnosis of a major depressive episode, namely depressed mood and loss of interest or pleasure (anhedonia). As depressed mood is a subjective feeling measurable through verbal interviews, it appears difficult to simulate and measure in animals. However, the inability to feel pleasure, which is highly correlated to the severity of the depressive episode, can be simulated in animals and measured through different behavioral paradigms described below. Consequently, anhedonia appears to be the most important symptom to reproduce in any attempt to realistically simulate depression.

Etiological factors in depression

Numerous factors have been implicated in the etiology of depression: psychological factors, such as adverse life events, chronic stress, and negative experience during childhood; personality traits, such as introversion and impulsivity; biological factors, such as genetic background; and a series of physical diseases and medications.[3,4] In certain cases, precipitating factors can be clearly identified as, for instance, in seasonal affective disorders or postpartum depression. However, in most cases, depression seems to result from the accumulation of several different risk factors.[5]

The probability of entering into a depressive episode is increased 5 to 6 times during the 6-month period following the appearance of stressful events.[6] A chronic mild stress regimen is recognized as a particularly powerful predisposing factor.[7] Unemployment and financial difficulties are associated with a high risk of depression. This type of events (uncontrollable stress) can generate feelings of worthlessness and guilt (symptoms of a major depressive episode) resulting in an inability to react. This type of chronic, low-grade stress is a more efficacious precipitant of depression than intense acute stressors.[4] One of the most significant effects of stress is a decreased performance in motivated behaviors. The hypothesis according to which depression results from a reduction in the activity of the reward systems is central to a number of theories on depression. In addition, the inability to react to normally pleasant events constitutes one of the two core symptoms of depression.[8] Thus, demonstration in rats of a chronic, mild, unpredictable stress-induced decrease in reward offers one of the most appropriate simulations of some aspects of human depression.

Chronic mild stress-induced anhedonia in rats

In order to develop a realistic simulation of depressive states in animals, a double problem has to be solved: how to induce an anhedonic state in laboratory rats, and how to adequately and reproducibly measure this anhedonic state.

How can an anhedonic state be induced in the laboratory rat?

In 1981, Katz and collaborators developed a procedure whereby rats were submitted to a variety of chronic,

unpredictable stressors such as electric shocks, immersion in cold water, tail pinch, etc. Following a week of such a stress regimen, animals exhibited behavioral deficits and hormonal changes that could be prevented by administration of antidepressants, but not by other psychotropic substances. Unlike control animals, the chronically stressed animals did not increase drinking when saccharine or sucrose was added to their drinking water to enhance palatability.[9,10] This observation was particularly important as it implied that this chronic stress regimen was able to induce dysfunctioning of the reward systems. This abnormality in the drinking behavior could reflect the development of an anhedonic state in animals.

Later, Willner adapted this procedure by using less severe stressors which were supposed to provide a better analogy with mild unpredictable stressors encountered in daily life.[11] Rats exposed to such a mild stress procedure progressively develop a reduced sensitivity to reward as evaluated by reduction in sucrose consumption. This behavioral deficit could be restored by chronic treatment with antidepressants. Considering that chronic low-grade stressors are an important factor in the etiology of depression, we have adapted Willner's procedure to our laboratory needs. This stress procedure used in all experiments reported here is described in *Table I*.[12]

How can an anhedonic state be evaluated in laboratory rats?

Different behavioral paradigms can be used to evaluate sensitivity to reward in animals: sucrose consumption, place conditioning, and self-stimulation behavior.

Initially, Willner used sucrose consumption measurement. He showed that the chronic mild stress procedure induced a substantial reduction in consumption and/or preference of sucrose solutions.[11] This reduction was interpreted as reflecting a decreased sensitivity to reward in stressed animals. However, sucrose consumption can vary from one experiment to another and can be influenced by body weight loss resulting from the stress.[13]

Papp et al[14] have used the place preference paradigm to study the stress effects on reward induced by sweet solutions or amphetamine. In this paradigm, pleasure intensity is monitored by the preference exhibited by the animals for an environment previously associated with appetitive properties of food or amphetamine. These authors have shown that chronic mild stress elicited a decrease in the place preference behavior, which was interpreted as indicating an altered response to pleasure. However, these data could also be explained by a reduced ability of stressed animals to associate reinforcing stimulus with the environment where this stimulus is presented. Deficits in associative learning have been observed in animals exposed to electric shocks[15] and subtle alterations of attention induced by "nonpertinent" stimuli have also been reported.[16]

Self-stimulation behavior is a very useful way for studying positive reinforcements and motivational or hedonic states. The self-stimulation technique allows a rat implanted with an electrode in a particular reward area of the brain to self-administer weak electrical pulses. Such stimulation can have very intense reinforcing properties. Thus, the greater the rewarding properties of the stimulation, the more the rat will self-stimulate. The threshold for self-stimulation behavior can thus be used as an index of its hedonic/anhe-

	Morning	Afternoon
Monday	8 AM 1-h confinement in restricted space	1 PM 1-h confinement in restricted space 4 PM overnight illumination
Tuesday	8 AM self-stimulation 11 AM 1-h confinement in restricted space	2 PM 1-h confinement in restricted space 4 PM food and water deprivation for 18 h
Wednesday	8 AM access to restricted food for 2 h	1 PM 1-h confinement in restricted space 4 PM water deprivation for 18 h
Thursday	8 AM exposure to empty bottle for 1 h 11 AM 1-h confinement in restricted space	2 PM 1-h confinement in restricted space 4 PM group-housed in soiled cage for 18 h
Friday	8 AM self-stimulation 11 AM 1-h confinement in restricted space	4 PM reversed light/dark cycle throughout the weekend

Table I. Chronic, mild, unpredictable stress procedure.

Reproduced from reference 12: 5-HT_{2C} receptor agonists exhibit antidepressant-like properties in the anhedonia model of depression in rats. *Eur Neuropyschopharmacol*. 1996;6:169-175.

donic state.[17] An increase in this threshold will indicate a decreased sensitivity to reward. By allowing stimulation of the mesocorticolimbic structures, it is possible to obtain very intense self-stimulation behavior because this stimulation activates directly the neuronal substrates involved in motivational processes. In our model, self-stimulation behavior induced by activation of the ventral tegmental area was used because corticolimbic projections of this brain structure constitute the main source of the dopaminergic innervation of the brain, which plays a major role in motivational and rewarding processes.[18]

Effects of chronic mild stress on sensitivity to pleasure in rats

By using a chronic, unpredictable, mild stress regimen as the etiological factor and variations of ventral tegmentum self-stimulation threshold as the anhedonia scale, it was shown that rats exposed for 3 weeks to such a stress regimen exhibited an increase in self-stimulation threshold *(Figure 1)*, ie, a decrease in their sensitivity to pleasure. This effect progressively developed over the first 2 weeks of stress, lasted until the end of the stress period, and gradually disappeared thereafter. Nonstressed animals did not develop such an anhedonic state. This increase in self-stimulation threshold is compatible with a decrease in the reinforcing efficacy of the stimulation, reflecting the gradual development of an anhedonic state induced by stress. The decreased sensitivity to reinforcing stimuli as well as the progressive development of stress effects resemble certain aspects of depression in man. These observations already provide this animal model of depression with a certain degree of theoretical validity.

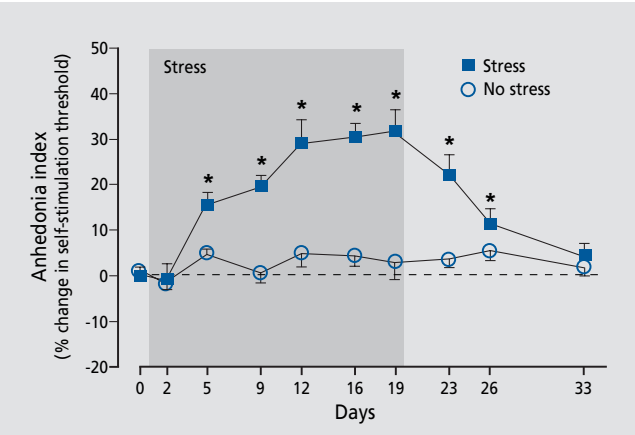

Figure 1. Anhedonia induced by a chronic mild stress regimen in rats. Variations in self-stimulation threshold in stressed (blue squares) and nonstressed (open circles) animals are shown as a function of stress exposure time (shaded area). Asterisks indicate statistically significant difference (Student *t* test, $P<0.05$) with baseline value measured before the stress period (day 0).

Validation of the anhedonia model

Predictive validity

The next step consisted in verifying whether the various types of clinically effective antidepressant treatments would be active in this model, and whether medications failing to have antidepressant effects (such as anxiolytics, antipsychotics, and analgesics) would be inactive. Several representative drugs of the different classes of antidepressants were tested with respect to their preventative or curative effects on stress-induced anhedonia. When rats were stressed and simultaneously treated with a tricyclic antidepressant drug (desipramine[19]) or a type A monoamine oxidase (MAO) inhibitor (moclobemide[20]), the anhedonia index did not vary (as in nonstressed animals), whereas stressed placebo-treated rats progressively developed an anhedonic state *(Figure 2)*.

These substances prevent the development of a hedonic deficit in stressed rats whereas they remain without effect in nonstressed animals. These results are in line with clinical observations. Indeed, tricyclic antidepressants and MAO inhibitors are effective in depressed patients but do not modify mood in nondepressed individuals.

These first experiments used preventative treatments. This type of manipulation does not optimally simulate the clinical situation where patients consult a practitioner once they are already depressed and should therefore undergo a curative therapy. Thus, the predictive validity of this animal model was further tested by evaluating a curative treatment with a representative of the atypical antidepressants (mianserin[21]). As shown in *Figure 3* (upper part), the chronic mild stress procedure resulted in an increase in self-stimulation threshold in both groups of stressed rats. This anhedonia progressively developed over 2 weeks to then reach a plateau. When stressed anhedonic animals were treated with mianserin from day 22 to day 38 of the stress period, the increase in self-stimulation threshold was completely abolished after about 10 days of treatment. When stressed anhedonic rats were treated with placebo during the same period of time, their anhedonic state did not normalize. This experiment has proven that this animal model was able to detect a further category of

antidepressant drugs and was appropriately responding to curative treatment of the anhedonic state.

In summary, these pharmacological experiments have demonstrated two important features: (i) chronic treatment is necessary to obtain an adequate antidepressant effect in stressed animals; and (ii) in nonstressed rats, the antidepressant treatment does not modify the self-stimulation behavior. These observations point to the similarity with the clinical situation where (i) in depressed patients, at least 2 to 3 weeks of treatment are necessary before observing a significant mood improvement; and (ii) antidepressant drugs do not modify mood in nondepressed individuals.

These pharmacological data allow chronic mild stress-induced anhedonia in rats to be considered as a simulation of human depression exhibiting a fair predictive validity for drug therapy of affective disorders. In order to further substantiate this validity, we tested the effects of a non-pharmacological treatment of depression, namely electroshock therapy. This treatment is used in severe cases of depression not responding to classic antidepressant medication. Electroshock therapy is recognized as being more efficacious and more rapidly acting than chemotherapy.[22,23] Thus, we tested the effects of electroshock treatment in anhedonic rats.[24] Results are presented in *Figure 4*.

In both groups of animals, the stress regimen induced an anhedonic state that gradually developed over a 2-week period. When "depressed" animals were submitted to an electroshock on day 21, their anhedonic state was com-

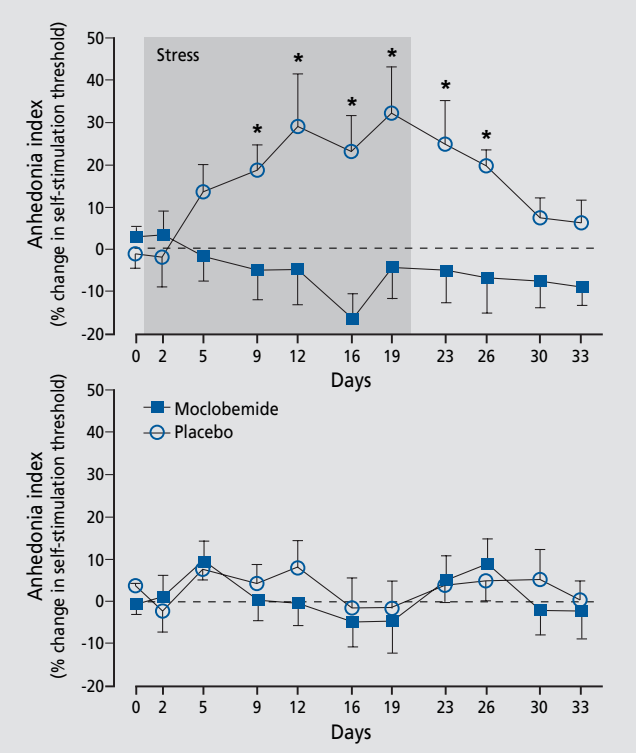

Figure 2. Preventative effects of a monoamine oxidase inhibitor (moclobemide, 20 mg/kg bid intraperitoneally) on stress-induced anhedonia. **Top**: Variations in self-stimulation threshold in stressed rats administered of moclobemide (blue squares) or placebo (open circles) as a function of stress exposure time (shaded area). **Bottom**: Variations in self-stimulation threshold in nonstressed moclobemide (blue squares) or placebo (open circles)–treated rats.[20] *Significantly different from prestress control values.

Reproduced from reference 20: Moreau JL, Jenck F, Martin JR, Motas P, Haefely W. Effects of moclobemide, a new generation reversible MAO-A inhibitor, in a novel animal model of depression. *Pharmacopsychiatry*. 1993;26:30-33. Copyright © 1993, Thieme Medical Publishers.

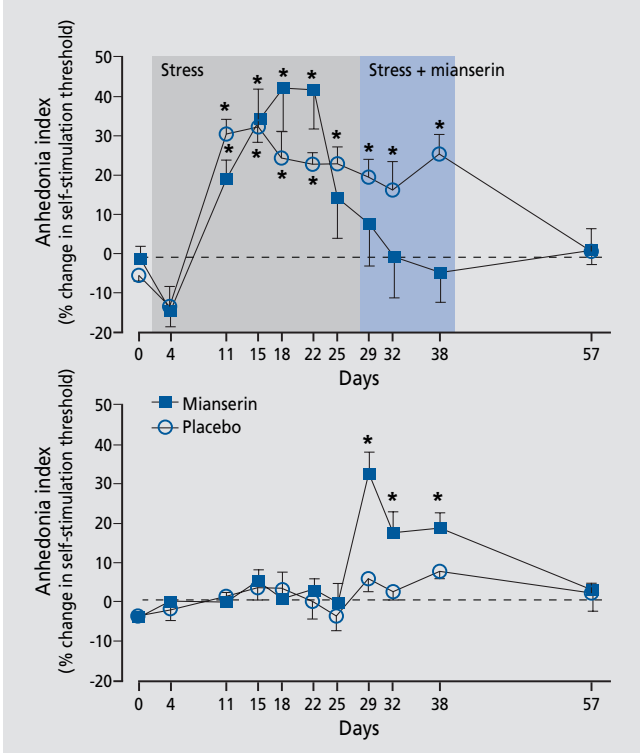

Figure 3. Curative effects of an atypical antidepressant (mianserin, 5 mg/kg intraperitoneally) on stress-induced anhedonia. **Top**: Variations in self-stimulation threshold in stressed (day 0 to day 38) rats treated (day 22 to day 38) with mianserin (blue squares) or placebo (open circles) as a function of stress exposure time (shaded area). **Bottom**: Variations of self-stimulation threshold in nonstressed rats treated (day 22 to day 38) with mianserin (blue squares) or placebo (white circles).[21] *Significantly different from prestress control values.

Reproduced from reference 20: Moreau JL, Bourson A, Jenck F, Martin JR, Mortas P. Curative effects of the atypical antidepressant mianserin in the chronic mild stress-induced anhedonia model of depression. *J Psychiatry Neurosci*. 1994;19:51-56. Copyright © 1994, Canadian Medical Association.

pletely and very rapidly reversed. In contrast, anhedonia of stressed animals submitted to sham shocks was not significantly diminished. Electroshock treatment was found to be much more rapid than antidepressant medications. These results provide an interesting parallel with the clinical situation where, in certain cases, nonresponder depressed patients exhibited a rapid and profound mood elevation following electroconvulsive therapy. Indeed, it has long been known that patients responding to electroshocks often exhibit a rapid loss of their depressive symptomatology.[25]

A final step in evaluating the predictive validity of this simulation consisted in verifying its specificity for antidepressant treatments. To this purpose, the effects of the antipsychotic drug risperidone were evaluated in stressed animals. As shown in *Figure 5*,[26] all stressed rats developed an anhedonic state, whether they were treated with placebo or with risperidone. Preventative treatment with this antipsychotic drug remained inefficient in suppressing stress-induced anhedonia. Risperidone by itself increased self-stimulation threshold in nonstressed animals. This could explain the loss of an antianhedonic effect in stressed animals. Risperidone blocks both dopaminergic D_2 and serotonergic 5-HT_2 receptors. Numerous studies have shown that antidopaminergic drugs (neuroleptics) decrease the self-stimulation threshold in naive animals.

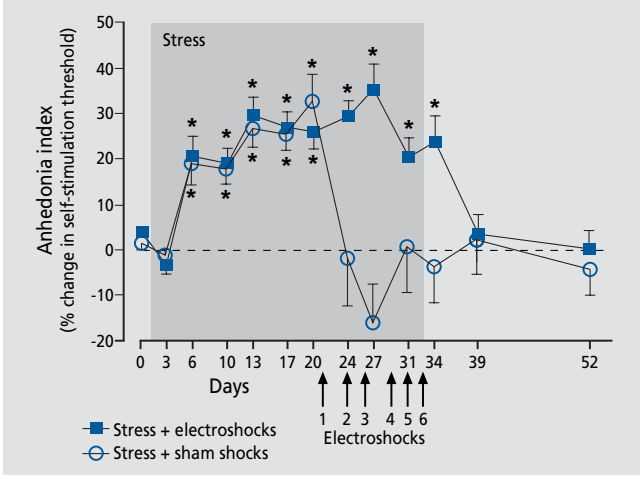

Figure 4. Curative effects of electroshock treatment on stress-induced anhedonia. Variations of self-stimulation threshold in stressed (from day 1 to day 33) rats treated (from day 21 to day 33) with 6 electroshocks (open circles) or sham shocks (blue squares) as a function of stress exposure time (shaded area).[24] *Significantly different from prestress control values.

Reproduced from reference 24: Moreau JL, Scherschlicht R, Jenck F, Martin JR. Chronic mild stress-induced anhedonia model of depression: sleep abnormalities and curative effects of electroshock treatment. *Behav Pharmacol*. 1995;6:682-687. Copyright © 1995, Lippincott, Williams & Wilkins.

However, this property is unlikely to explain the lack of effect of risperidone on stress-induced anhedonia, as mianserin abolished this anhedonia and decreased self-stimulation behavior in nonstressed animals These variations in self-stimulation thresholds in nonstressed rats most probably reflect subtle motor and/or cognitive deficits induced by those substances.

In summary, the results presented above have shown that the stress-induced anhedonia model is able to demonstrate the activity of electroshock and antidepressant drugs representing different biochemical mechanisms of action, whereas an antipsychotic drug was inactive. In addition, other related studies have shown that treatment with a tranquilizer (chlordiazepoxide), an analgesic (morphine), neuroleptics (haloperidol, chlorprothixene), or a psycho

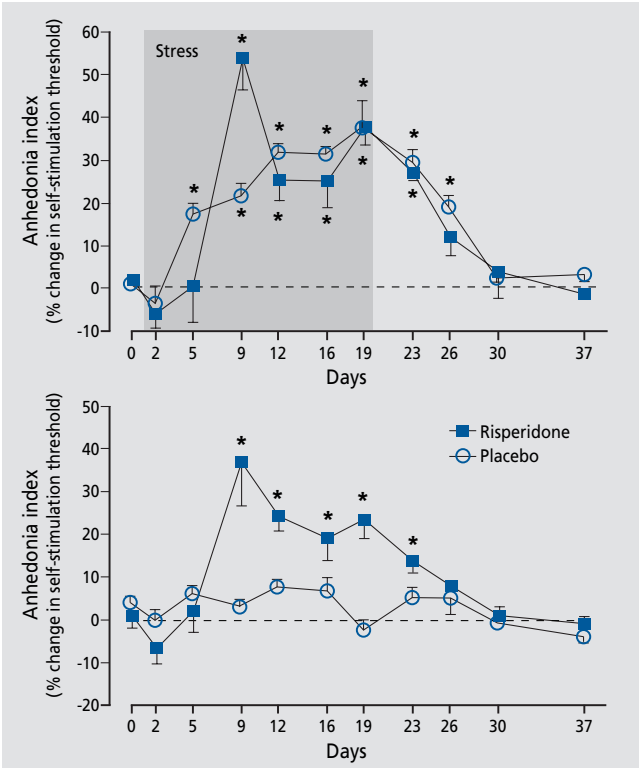

Figure 5. Lack of effect of an antipsychotic (risperidone) on stress-induced anhedonia.[26] **Top**: Variations of self-stimulation threshold in stressed rats treated with risperidone 0.3 mg/kg bid intraperitoneally (blue squares) or placebo (open circles) as a function of stress exposure time (shaded area). **Bottom**: Variations in self-stimulation threshold in nonstressed animals treated with risperidone 0.3 mg/kg bid intraperitoneally (blue squares) or placebo (open circles). *Significantly different from prestress control values.

Reproduced from reference 26: Moreau JL, Jenck F, Martin JR. Simulation of a core symptom of human depression in rats. *Curr Topics Pharmacol*. 1998;4:37-50. Copyright © 1998, Research Trends.

stimulant (amphetamine) also failed to reduce stress-induced anhedonia in rats.[27,28] Therefore, the anhedonia model offers a fair degree of predictive validity. This simulation of depression should allow, on the one hand, to detect novel types of substances acting on depressed mood to be developed, and, on the other hand, the rapidity of onset of those medications to be predicted.

Theoretical validity and aspect validity

Evaluating the theoretical and aspect validities of a simulation of depression consists in examining the degree of resemblance of the model with the syndrome it is supposed to reproduce. Ideally, an animal model should resemble the disease it simulates with regard to its etiology, symptomatology, treatment, and biological basis. In addition, a heuristic animal model should exhibit similarities with the core symptoms of a pathology rather than with the secondary symptoms.

Anhedonia, a core symptom of depression

As mentioned earlier, *DSM-IV* defines two core symptoms in the diagnosis of a depressive episode: depressed mood (a subjective feeling impossible to simulate in animals) and anhedonia. The choice of anhedonia as an essential characteristic of this model provides this simulation with a remarkable aspect validity. Moreover, this simulation exhibits other similarities with depression. First, it can show a curative effect of antidepressant treatment on hedonic deficit, and not only a prophylactic effect. Second, the stress regimen continues during the treatment period, like the clinical situation, as there is usually no major change in the life conditions of a depressed patient that could be associated with treatment. Third, the time course of the antidepressant effect (10 to 20 days) in the anhedonia model corresponds to the time course observed clinically. Finally, no change is observed in control animals, as is the case for healthy volunteers in which antidepressants remain without effect on mood.

The chronic, mild, unpredictable stress regimen

This model also offers a realistic simulation of depression, because it utilizes a chronic, mild, unpredictable stress procedure. Many studies have involved chronic mild stressors as important factors for the genesis of a depressive episode. Moreover, it has been shown that the consequences of mild stressors are exacerbated after a stressful life event.[29] The anhedonia simulation in rats offers a reasonable approximation of stressful events encountered in daily life. The more conventional stress models, which use only one confrontation with severe stressors, seem less appropriate to reproduce certain aspects of depression. In summary, this simulation can be considered as providing a better aspect validity with respect to the etiological role of stressful life events, compared with models using acute and more severe stressors.

Biological markers of depression

We have also shown that the regimen of chronic mild stress used in this simulation was able to induce abnormalities in certain sleep parameters.[24] As shown in *Figure 6*, such a stress regimen elicits a decrease in the latency to the first episode of paradoxical rapid eye movement (REM) sleep, as well as an increase in the number of episodes of this sleep stage. These abnormalities progressively develop as they appear only 2 weeks after initiation of the stress regimen.
These results are important because they reproduce clinical findings. Indeed, several studies have shown sleep abnormalities in depressed patients.[30-33] These abnormalities also consist in a decreased latency for REM sleep and an increase in its frequency. These abnormalities are considered by a number of clinicians as biological markers of depression. A decrease in REM sleep latency is perhaps the most frequent observation performed in depressed patients.[34,35] It is recognized as a potential marker for endogenous depression.
In summary, the stress-induced anhedonia model exhibits a solid aspect validity in its etiology, symptomatology, treatment, and biological bases. The results clearly suggest a causal relationship between chronic mild stress and the anhedonia symptom. This relationship has been confirmed by a study in humans that showed that endogenous depressed patients experience the severity of stressful events in an exaggerated manner.[36] The clinical confirmation of a direct relationship between chronic mild stress and anhedonia reinforces the validity of the simulation and its heuristic value.

Conclusion

The similarities between the stress-induced anhedonia model in rats and certain aspects of depressive disorder in humans are illustrated by the following main results *(Table II)*.

Theoretical validity

The stress procedure used in these studies was able to induce a decrease in sucrose consumption and/or preference, a decrease in the ability to associate pleasurable events with a particular environment (place preference), and an increase in the current threshold necessary to elicit self-stimulation behavior. These results obtained by different research groups using different strains of animals strengthen the idea that a chronic, mild, unpredictable stress regimen induces a decreased sensitivity to pleasure, ie, an anhedonic state. Anhedonia is one of the two core symptoms of depression.

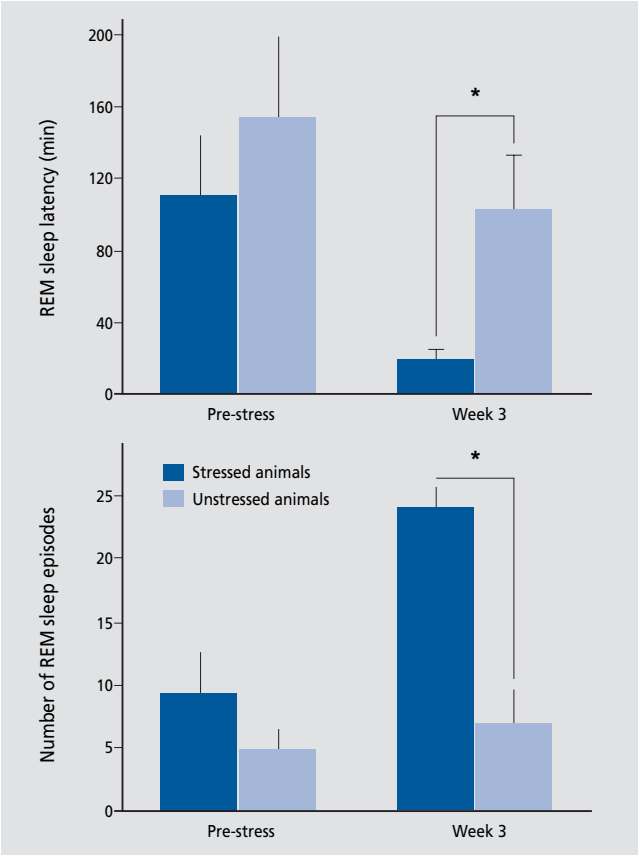

Figure 6. Paradoxical sleep abnormalities in chronically stressed animals. Decrease in latency and increase in number of episodes of paradoxical sleep in rats exposed to the chronic mild stress procedure for 3 weeks (dark blue bars) compared with control unstressed animals (light blue bars).[24] REM, rapid eye movement. *Significantly different from prestress control values. Reproduced from reference 24: Moreau JL, Scherschlicht R, Jenck F, Martin JR. Chronic mild stress-induced anhedonia model of depression: sleep abnormalities and curative effects of electroshock treatment. *Behav Pharmacol*. 1995;6:682-687. Copyright © 1995, Lippincott, Williams & Wilkins.

Aspect validity

In addition to inducing an anhedonic state, the chronic mild stress regimen triggers the development of several other symptoms of depression. Indeed, it is able to decrease sexual and aggressive behavior,[37] inhibit locomotor activity, and induce a phase advance shift in circadian rhythm,[41] elicit a body weight loss, hypertrophy of the adrenals,[26] hypersecretion of corticosterone,[38] and sleep abnormalities.[24] However, this stress regimen did not induce particular anxiety symptoms in two animal models of anxiety, the elevated plus-maze and the social interaction tests.[37] Therefore, this simulation elicits behavioral and physiological abnormalities found in depression, and these effects seem to have some specificity for depressive-like behaviors.

Predictive validity

The different types of antidepressant drugs did not modify reinforced behaviors in control nonstressed animals. Medications effective in antagonizing stress-induced anhedonia include representatives of the tricyclics[11,19] monoamine reuptake inhibitors such as fluoxetine and maprotiline,[27] inhibitors of monoamine oxidase such as moclobemide and brofaromine,[20,28] and atypical antidepressants such as mianserin.[21,39] Electroconvulsive shocks[24] and lithium[40] are also active in this model. The antagonism of stress-induced anhedonia requires 2 to 4 weeks of treatment, similar to the time course of antidepressant drugs in humans. Inefficacious substances include representatives of tranquilizers such as chlordiazepoxide[27]; antipsychotics such as risperidone (see above), haloperidol, and chlorprothixene; psychostimulants such as amphetamine; and analgesics such as morphine.[28] Therefore, this simulation appears as specific and selective in its response to all categories of clinically used antidepressant treatments, and in its lack of response to other nonantidepressant psychotropics.

In conclusion, among all animal models of depression, stress-induced anhedonia is probably the best characterized simulation that most appropriately reflects certain fundamental aspects of human depression. One of the most important aspects of animal models is to suggest hypotheses about the functioning and the involvement of particular neurotransmission systems and/or particular brain areas in psychiatric disorders.[42] This model should allow a better understanding of some of the pathophysiological aspects of neuropsychiatric disorders in which anhedonia plays an essential role. ❑

	Depression in man	Anhedonia in rats
Symptoms	• Depressed mood	• Cannot be simulated
	• Loss of interest or pleasure	• Reduced sensitivity to reward
	• Decreased sex drive	• Decreased sexual activity
	• Low self-esteem	• Decreased aggressive behavior
Risk factors	• Stressful life events	• Chronic mild stress
	• Social isolation in childhood	• Isolation-reared animals are more vulnerable to chronic mild stress
Biological markers	• Sleep abnormalities	• Sleep abnormalities
	• Corticosterone hypersecretion	• Corticosterone hypersecretion
Active treatments	• Tricyclics	• Amitriptyline, imipramine, desipramine
	• Atypicals	• Maprotiline, mianserin
	• SSRIs	• Fluoxetine, citalopram, sertraline
	• SNRIs	• Venlafaxine
	• MAO inhibitors	• Moclobemide, brofaromine
	• Electroconvulsive therapy	• Electroshock treatment
Ineffective treatments	• Anxiolytics	• Chlordiazepoxide
	• Psychostimulants	• Amphetamine
	• Antipsychotics	• Risperidone, haloperidol, chlorprothixene
	• Analgesics	• Morphine

Table II. Similarities between main features of a depressive episode in man and chronic mild stress-induced anhedonia in rats. Data in animals are a compilation of results found in the following publications: 11, 14, 19-21, 24, and 36-40. MAO, monoamine oxidase; SNRIs, selective noradrenaline reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.

REFERENCES

1. Mckinney WT. Animal models of depression: an overview. *Psychiatr Dev*. 1984;2:77-96.
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association; 1994.
3. Akiskal HS. A developmental perspective on recurrent mood disorders: a review of studies in man. *Psychopharmacol Bull*. 1986;22:579-586.
4. Willner P. *Depression: a psychobiological synthesis*. New York, NY: Wiley; 1985.
5. Aneshensel CS, Stone JD. Stress and depression: a test of the buffering model of social support. *Arch Gen Psychiatry*. 1982;39:1392-6.
6. Lloyd C. Life events and depressive disorder reviewed. II. Events as precipitating factors. *Arch Gen Psychiatry*. 1980;37:541-548.
7. Billings AG, Cronkite RC, Moos RH. Social-environmental factors in unipolar depression: comparisons of depressed patients and non-depressed controls. *J Abnorm Psychol*. 1983;92:119-133.
8. Nelson JC, Charney DS. The symptoms of major depression. *Am J Psychiatry*. 1981;138:1-13.
9. Katz RJ. Animal model of depression: pharmacological sensitivity of a hedonic deficit. *Pharmacol Biochem Behav*. 1982;16:965-968.
10. Katz RJ, Sibel M. Animal model of depression: tests of three structurally and pharmacologically novel antidepressant compounds. *Pharmacol Biochem Behav*. 1982;16:973-977.
11. Willner P, Towell, A, Sampson D, et al. Reduction of sucrose preference by chronic unpredictable mild stress, and restoration by tricyclic antidepressant. *Psychopharmacology*. 1987;93:358-364.
12. Moreau JL, Bos M, Jenck F, Martin JR, Mortas P, Wichmann J. *Eur Neuropsychopharmacol*. 1996;6:169-175.
13. Matthews K, Forbes N, Reid IC. Sucrose consumption as an hedonic measure following chronic unpredictable mild stress. *Physiol Behav*. 1995;57:241-248.
14. Papp M, Willner P, Muscat R. An animal model of anhedonia: attenuation of sucrose consumption and place preference conditioning by chronic unpredictable mild stress. *Psychopharmacology*. 1991;104:255-259.
15. Rosellini RA, De Cola JP, Plonsky M, et al. Uncontrollable shock proactively increases sensitivity to response-reinforcer independence in rats. *J Exp Psychol Anim Behav Process*. 1984;10:346-359.
16. Minor TR, Pelleymounter MA, Maier SF. Effects of task-irrelevant cues and reinforcement delay on choice-escape learning following inescapable shock: evidence for a deficit in selective attention. *J Exp Psychol*. 1988;10:543-556.
17. Markou A, Koob GF. Postcocaine anhedonia: an animal model of cocaine withdrawal. *Neuropsychopharmacology*. 1991;4:17-25.
18. Fibiger HC, Phillips AG. Role of catecholamine transmitters in brain reward systems: implications for the neurobiology of affect. In: Engel J, Oreland L, eds. *Brain Reward Systems and Abuse*. New York, NY: Raven Press; 1987:61-74.
19. Moreau JL, Jenck F, Martin JR, et al. Antidepressant treatment prevents chronic mild stress-induced anhedonia as assessed by ventral tegmentum self-stimulation behavior in rats. *Eur Neuropsychopharmacol*. 1992;2:43-49.
20. Moreau JL, Jenck F, Martin JR, Mortas P, Haefely W. Effects of moclobemide, a new generation reversible MAO-A inhibitor, in a novel animal model of depression. *Pharmacopsychiatry*. 1993;26:30-33.
21. Moreau JL, Bourson A, Jenck F, Martin JR, Mortas P. Curative effects of the atypical antidepressant mianserin in the chronic mild stress-induced anhedonia model of depression. *J Psychiatry Neurosci*. 1994;19:51-56.
22. Avery D, Winokur G. The efficacy of electroconvulsive therapy and antidepressants in depression. *Biol Psychiatry*. 1977;12:507-523.
23. Fink M. Indication for the use of electroconvulsive therapy. *Psychopharmacol Bull*. 1994;30:269-275.
24. Moreau JL, Scherschlicht R, Jenck F, Martin JR. Chronic mild stress-induced anhedonia model of depression: sleep abnormalities and curative effects of electroshock treatment. *Behav Pharmacol*. 1995;6:682-687.

Simulación del síntoma depresivo anhedonia en animales

Uno de los dos síntomas centrales en la depresión es la anhedonia, la pérdida del interés o del placer en las actividades diarias. Se ha reconocido que los acontecimientos vitales estresantes actúan como factores predisponentes en la etiología de la depresión. Las ratas sometidas a una situación de estrés crónico, leve e impredecible exhiben déficits conductuales que consisten en una pérdida de sensibilidad ante la recompensa, tales como disminución en el consumo de sucrosa, disminución de la capacidad para asociar recompensas con un ambiente característico y una sensibilidad disminuida a la estimulación eléctrica cerebral gratificante. La conducta normal se restituye mediante el tratamiento crónico con antidepresivos o electrochoques. Los animales estresados crónicamente también presentan trastornos del sueño que recuerdan lo que se ha observado en pacientes depresivos y que se ha reconocido como marcadores biológicos de la depresión. De este modo, la anhedonia inducida por el estrés en las ratas representa un modelo animal original de algunos aspectos de la depresión en humanos y ofrece elementos convergentes de validez biológica, sintomatológica, etiológica y terapéutica. Esta simulación de la depresión puede probar su utilidad para una mejor comprensión de los mecanismos fisiopatológicos involucrados en los trastornos depresivos.

Simulation chez l'animal de l'anhédonie, symptôme de dépression

Un des deux principaux symptômes de la dépression est l'anhédonie, ou manque d'intérêt ou de plaisir dans les activités quotidiennes. Les événements stressants de la vie sont reconnus comme des facteurs prédisposants dans l'étiologie de la dépression. Des rats soumis à un régime de stress chronique, léger et imprévisible montrent des déficits du comportement importants compatibles avec une perte de réactivité à la récompense, comme une diminution de la consommation de sucre, une moins bonne capacité à associer les récompenses avec un environnement particulier, et une diminution de la sensibilité à la stimulation électrique récompensante du cerveau. Une conduite normale est restaurée par un traitement chronique par antidépresseurs ou électrochocs. Des animaux stressés de façon chronique montrent également des troubles du sommeil ressemblant à ceux observés chez les patients déprimés et reconnus comme des marqueurs biologiques de la dépression. Ainsi, une anhédonie induite par le stress chez le rat représente un modèle animal original de certains aspects de la dépression humaine offrant des éléments convergents de valeur biologique, symptomatologique, étiologique et thérapeutique. Cette simulation de la dépression peut se montrer utile pour une meilleure compréhension des mécanismes physiopathologiques impliqués dans les troubles dépressifs.

25. Abrams R. Out of the blue: the rehabilitation of electroconvulsive therapy. *Sciences (New York)*. 1989;29:24-30.
26. Moreau JL, Jenck F, Martin JR. Simulation of a core symptom of human depression in rats. *Curr Topics Pharmacol*. 1998;4:37-50.
27. Muscat R, Papp M, Willner P. Reversal of stress-induced anhedonia by the atypical antidepressants fluoxetine and maprotiline. *Psychopharmacology*. 1992;109:433-438.
28. Papp M, Moryl E, Willner P. Pharmacological validation of the chronic mild stress model of depression. *Psychopharmacology*. 1996;296:129-136.
29. Brown GW. Life events and affective disorders: replications and limitations. *Psychosom Med*. 1993;55:248-259.
30. Gillin JC, Wyatt RJ, Fram D, et al. The relationship between changes in REM sleep and clinical improvement in depressed patients treated with amitriptyline. *Psychopharmacology*. 1978;59:267-272.
31. Kupfer DJ, Thase ME. The use of the sleep laboratory in the diagnosis of affective disorders. *Psychiatr Clin North Am*. 1983; 6: 3-25.
32. Reynolds CF, Kupfer DJ, Houck PR, et al. Reliable discrimination of elderly depressed and demented patients by electroencephalographic sleep data. *Arch Gen Psychiatry*. 1988;45:258-264.
33. Steiger A, von Bardeleben U, Guldner J, Lauer C, Rothe B, Holsboer F. The sleep EEG and nocturnal hormonal secretion studies on changes during the course of depression and on effects of CNS active drugs. Prog *Neuropsychopharmacol Biol Psychiatry*. 1993;17:125-137.
34. Reynolds CF, Kupfer DJ. Sleep research in affective illness, state of the art circa 1987. *Sleep*. 1987;10:199-215.
35. Rush AJ, Erman MK, Giles DE. Polysomnographic findings in recent drug-free and clinically remitted depressed patients. *Arch Gen Psychiatry*. 1986;43:878-884.
36. Willner P, Wilkes M, Orwin O. Attributional style and perceived stress in endogenous and reactive depression. *J Affect Dis*. 1990;18:281-287.
37. D'aquila P, Brain P, Willner P. Effects of chronic mild stress on performance in behavioral tests relevant to anxiety and depression. *Physiol Behav*. 1994;56:861-867.
38. Ayensu WT, Pucilowski O, Mason GA, et al. Effects of chronic mild stress on serum complement activity, saccharin preference and corticosterone levels in Flinders lines of rats. *Physiol Behav*. 1995;57:165-169.
39. Cheeta S, Broekkamp CLE, Willner P. Stereospecific reversal of stress-induced anhedonia by mianserin and its (+) enantiomer. *Psychopharmacology*. 1994;116:523-528.
40. Sluzewska A, Nowakowska E. The effects of carbamazepine, lithium and ketoconazole in chronic mild stress model of depression in rats. *Behav Pharmacol*. 1994;5(suppl 1):86.
41. Gorka Z, Moryl E, Papp M. Chronic mild stress influences the diurnal activity rhythms in rats. *Behav Pharmacol*. 1994;5(suppl 1):88.
42. Thiebot MH, Martin P, Puech AJ. Animal behavioural studies in the evaluation of antidepressant drugs. *Br J Psychiatry*. 1992;15:44-50.