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REVIEW

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Validity, reliability and utility of the chronic mild stress model of depression: a 10-year review and evaluation

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Abstract This paper evaluates the validity, reliability and utility of the chronic mild stress (CMS) model of depression. In the CMS model, rats or mice are exposed sequentially, over a period of weeks, to a variety of mild stressors, and the measure most commonly used to track the effects is a decrease in consumption of a palatable sweet solution. The model has good predictive validity (behavioural changes are reversed by chronic treatment with a wide variety of antidepressants), face validity (almost all demonstrable symptoms of depression have been demonstrated), and construct validity (CMS causes a generalized decrease in responsiveness to rewards, comparable to anhedonia, the core symptom of the melancholic subtype of major depressive disorder). Overall, the CMS procedure appears to be at least as valid as any other animal model of depression. The procedure does, however, have two major drawbacks. One is the practical difficulty of carrying out CMS experiments, which are labour intensive, demanding of space, and of long duration. The other is that, while the procedure operates reliably in many laboratories, it can be difficult to establish, for reasons which remain unclear. However, once established, the CMS model can be used to study problems that are extremely difficult to address by other means.

Key words Animal model of depression
Chronic mild stress · Predictive validity · Face validity
Construct validity · Reliability · Rat

Introduction

Research into the mechanisms underlying antidepressant drug action must engage with two critical issues. First, antidepressant drugs are largely devoid of mood-elevating effects in normal individuals. This means that the relevance of studies carried out in normal animals is questionable, and animal models of depression are indispensible research tools. Second, the efficacy of antidepressants requires chronic treatment over a period of weeks. This means that if animal models are to be used to study antidepressant actions over a clinically relevant time scale, the behavioural symptoms induced in the model must persist for a period of weeks.

In addition to their role in the discovery of new and improved antidepressants, animal models of depression are in principle useful for a variety of other purposes, including the provision of insights into the neurobiology and pathophysiology of depression. However, this imposes a further requirement: the data derived from animal models are likely to be of value only to the extent that the models are valid. The procedures for validating animal models of psychiatric disorders have been discussed in detail elsewhere (Willner 1984, 1990); they include consideration of predictive validity (which concerns primarily the correspondence between drug actions in the model and in the clinic), face validity (phenomenological similarities between the model and the disorder), and construct validity (a sound theoretical rationale). Some desirable features in an animal model of depression are that the model should respond appropriately to antidepressant drugs; should employ realistic inducing conditions; and should model a core symptom of the disorder. While several of the available models have a reasonable pharmacological profile, with relatively few false positives and false negatives, very few models perform well against all three sets of validating criteria, and even fewer include the additional feature of chronicity (Willner 1984, 1990).

The chronic mild stress model

Against this background, we set out some years ago to develop an animal model of depression that would be both valid as a simulation of depression, and chronic in its duration. The project was targetted at modelling anhedonia, which was the core symptom of the melancholic

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subtype of major depressive disorder in the diagnostic system prevailing at that time, DSM-III, and is again the core symptom of melancholia in the current diagnostic system, DSM-IV (American Psychiatric Association 1994). Anhedonia is defined as "the decreased capacity to experience pleasure of any sort" (Fawcett et al. 1983), and we aimed to model it by inducing a decrease in responsiveness to rewards.

The starting point for this project was a series of studies by Katz and colleagues, published in the early 1980s, in which rats were exposed sequentially to a variety of severe stressors. In most of these studies, the effects of stress were assessed by changes in open field behaviour, which were reversed specifically by chronic treatment with antidepressant drugs, but not by non-antidepressants (e.g. Katz and Hersh 1981; Katz et al. 1981a, b; Katz and Baldrighi 1982). However, in one study, it was observed that animals exposed to the chronic stress regime failed to increase their fluid consumption when saccharin or sucrose were added to their drinking water, and it was postulated that this might reflect a decrease in the hedonic impact of the sweetener (Katz 1982). This hypothesis was supported by the demonstration by Anisman and colleagues that uncontrollable footshock can lead to impairments of behaviour maintained by brain stimulation reward (Zacharko et al. 1983, 1984). In developing the chronic mild stress (CMS) procedure, we made two changes to the procedure described by Katz and colleagues: the severity of the stressors employed was greatly reduced, and hedonic measures were made the primary focus of the model. The designation of the procedure as chronic mild stress indicates (i) that the behavioural changes induced by CMS may be observed over a period of several weeks of continuous administration; that is, habituation either does not occur, or occurs to only a limited extent; and (ii) that the individual stressors used do not include any of the severely stressful elements used by Katz and colleagues (e.g. intense footshock; cold water immersion; 48 h food/water deprivation).

In a typical experiment, rats (Willner et al. 1987, 1992) or mice (Monleon et al. 1994) are exposed sequentially to a variety of mild stressors (e.g. overnight illumination; periods of food and/or water deprivation; cage tilt; change of cage mate), which change every few hours over a period of weeks or months. The effectiveness of this procedure is usually monitored by tracking, over repeated tests, a decrease in the consumption of and/or preference for a palatable weak (1–2%) sucrose solution. As described below, other behavioural endpoints have also been studied, including brain stimulation reward threshold and place preference conditioning, as well as a variety of measures not directly related to reward sensitivity. CMS-induced behavioural deficits may be maintained for several months; however, normal behaviour is restored, during continued application of CMS, by chronic treatment with tricyclic or atypical antidepressants. This paper reviews the current status of the CMS model, in respect of its validity, reliability, and utility.

Construct validity

The theoretical rationale for the CMS model is that this procedure simulates anhedonia, a loss of responsiveness to pleasant events, which is a core symptom of depression and the defining feature of melancholia (American Psychiatric Association 1994). This rationale rests on two assumptions, that sucrose drinking is a valid measure of sensitivity to reward, and that CMS causes a generalized decrease in reward sensitivity, rather than a specific effect on responses to sweet tastes.

A number of alternative accounts of the decrease in sucrose drinking have been explored. Decreases in sucrose drinking cannot be explained by nonspecific changes in fluid consumption (e.g. decreased thirst), since the intake of plain water is unaffected by CMS (Muscat and Willner 1992), and the effects of CMS are seen in both single-bottle tests and in two-bottle (sucrose-water) preference tests (Willner et al. 1987; Muscat et al. 1988; Sampson et al. 1991; Pucilowski et al. 1993; Ayensu et al. 1995; D'Aquila et al. 1997). The calorie content of the sucrose also appears to be unimportant, since

1. Similar effects are seen in animals consuming calorie-free saccharin solutions (Willner et al. 1987; Ayensu et al. 1995);
2. Decreases in sucrose drinking can be seen in both food-deprived and non-deprived animals (Muscat and Willner 1992);
3. Decreases in sucrose drinking have been reported in studies in which the CMS procedure excluded periods of food and water deprivation (Griffiths et al. 1992; Muscat and Willner 1992; Cheeta et al. 1994; Dauge et al. 1996; Smadja 1996; Bertrand et al. 1997; Valverde et al. 1997);
4. Food intake is not decreased by CMS; in relation to this point, it is important to add that there is evidence that despite the fact that food intake is unchanged or even increased by CMS, the rewarding properties of food, are decreased, as indicated by an attenuation of (i) food-induced place preference conditioning (Papp et al. 1991; Muscat et al. 1992; Willner et al. 1994) and (ii) the acceleration of eating that is usually seen with very sweet diets (Sampson et al. 1992); and
5. The effects of CMS are concentration dependent: decreases are seen only when with dilute (calorie-poor) sucrose solutions, but not with concentrated (calorie-rich) solutions (Willner et al. 1991).

This last point merits further discussion, since it relates also to the previous point, that CMS decreases food reward but does not decrease food consumption. Sucrose drinking, in rodents, shows an inverted-U-shaped concentration-intake curve, with maximal intake at intermediate concentrations. The reasons for the decrease in intake at higher concentrations remain uncertain, but an aversive component can be excluded (Muscat et al. 1991). On the ascending limb of the concentration-intake curve, where CMS decreases sucrose drinking, intake is monotonically related to preference (Muscat et al. 1991);

however, on the descending limb of the concentration-intake curve, where CMS does not decrease sucrose drinking, intake is dissociated from preference: as concentration increases, intake decreases, but higher concentrations are always preferred in a choice test (Muscat et al. 1991). Three conclusions can be drawn from this analysis: first, that intake measures provide a measure of reward under some conditions but not under others; second, that it is necessary to evaluate whether the conditions are appropriate, in order to draw valid inferences; and third, that CMS experiments do use appropriate conditions (dilute sucrose solutions) under which changes in intake are monotonically related to changes in reward.

Two recent studies, from the same laboratory, have raised the possibility that changes in sucrose intake may be artefacts related to loss of body weight (Matthews et al. 1995; Forbes et al. 1996) This idea was advanced on the basis of the observation that CMS decreased both sucrose intake and body weight, but had no effect on a composite measure of sucrose intake per g of body weight. However, this observation is not confirmed in studies from eight other laboratories, where the proportional decrease in sucrose intake, in animals exposed to CMS, was much larger than the decrease in body weight, leading to significant decreases in the derivative measure, sucrose intake per g of body weight (Willner et al. 1996, where data from five laboratories are summarized; Charkrabarti et al. 1996; Hatcher et al. 1996; Valverde et al. 1997). A study in six mouse strains also reported that there was no relationship between the effects of CMS on consumption of a palatable diet and changes in body weight (Griffiths et al. 1992). The results reported by the Aberdeen group differ in a number of other respects from those observed in other laboratories: for example, in contrast to the decreases in sucrose/saccharin preference observed by others (e.g. Willner et al. 1987; Ayensu et al. 1995; D'Aquila et al. 1997), in Aberdeen, decreases in sucrose intake are not accompanied by decreases in sucrose preference (Matthews et al. 1995; Forbes et al. 1996). The most important discrepancy, however, is that the CMS procedure used by the Aberdeen group causes a massive (>20%) loss of body weight (Matthews et al. 1995; Forbes et al. 1996), more than twice as large as that observed elsewhere (0–10% in eight other laboratories: Charkrabarti et al. 1996; Hatcher et al. 1996; Willner et al. 1996; Valverde et al. 1997). This accounts for the discrepant negative findings of the Aberdeen group using the derivative measure of sucrose intake per g of body weight. This difference in the magnitude of the effects of CMS on body weight, in turn, arises because the CMS procedure used in Aberdeen (Matthews et al. 1995; Forbes et al. 1996) includes considerably longer periods of both food and water deprivation than the procedures used elsewhere. Long periods of food and water deprivation were used in the original version of the CMS procedure (Willner et al. 1987) but were subsequently removed, precisely in order to avoid the complications raised by extensive weight loss. In this important respect, the procedure used in Aberdeen (Matthews et al. 1995; Forbes et al. 1996), while derived from the original publication in this area (Willner et al. 1987), differs from the procedure used by all other laboratories currently working with the CMS model.

It should also be noted that, if weight loss does occur as a consequence of CMS, then the greater its extent, the lower the chance of observing a significant decrease in sucrose intake per g of body weight. However, it would be unwarranted to infer from a lack of significance in the sucrose/g measure that CMS had failed to decrease hedonic responsiveness. This may be illustrated by considering the application of a similar logic to the clinical situation. Depression is associated both with decreased hedonic responsiveness and with changes in body weight. The former may be relatively small, and the latter, relatively large. For example, two studies using the Fawcett-Clark Pleasure Capacity Scale reported a loss of hedonic responsiveness of 6% and 16% in two groups of diagnostically heterogeneous depressed patients (Fawcett et al. 1983). Some individuals lose weight when depressed while others gain weight, the direction of change being consistent across episodes (Stunkard and Rush 1974); in individuals who lose weight, the mean weight loss is around 5 kg, or approximately 7% of body weight; the maximum weight loss can be as much as 20% (Casper et al. 1985; Stunkard et al. 1990). Putting together these observations, it would not be surprising to calculate from clinical data that hedonic capacity per kg of body weight was unaltered in depression. However, it would be thoroughly misleading to infer from this finding that the depressed patients were not anhedonic. The relative measure has meaning only if changes in hedonic responsiveness are secondary to changes in body weight, which is not normally the case either in depression or in the CMS model. Indeed, there is evidence that decreases in body weight can actually mask the true extent of the CMS-induced decrease in sucrose intake, which in some circumstances are smallest among animals that lose the most weight (D'Aquila et al. 1997). Another important dissociation between these two measures is that chronic antidepressant treatment normalizes sucrose intake, but does not reverse CMS-induced weight loss (Willner et al. 1987).

A further finding reported by the Aberdeen group (Matthews et al. 1995; Forbes et al. 1996) was that sucrose intake was decreased in a group of animals exposed only to the food/water deprivation elements of the CMS procedure. Again, this conclusion is at variance with data from three previous studies demonstrating that sucrose intake is unaffected by a 20% weight reduction brought about by food deprivation and regular daily meal-feeding (Willner et al. 1991, 1996; Muscat and Willner 1992). These discrepancies may reflect a difference between the effects of meal-feeding and those of occasional unpredictable prolonged periods of deprivation: the latter procedure is presumably more stressful. The fact that sucrose intake is normal in meal-fed animals, despite extreme loss of body weight, suggests that hedonic changes may result from certain stressful dieting procedures, rather than from weight loss per se. It is also

possible that in some circumstances, extensive weight loss might indeed result in a secondary loss of hedonic responsiveness. It is known that severely restrictive diets are likely to cause symptoms of depression when body weight loss exceeds around 10% of normal (Keys 1950; Stunkard and Rush 1974); additionally, high rates of major depression are typically reported in patients with a primary diagnosis of anorexia nervosa (Herzog 1984; Piran et al. 1985; Laessle et al. 1987), and such depressions may resolve with effective treatment for weight loss (Herpetz-Dahlman and Remschmidt 1989). However, in all of these cases, it is impossible to separate the influence of weight loss per se from that of the attendant stress. The possibility that certain dieting procedures may provide a simple means of inducing anhedonia merits investigation. In particular, it would be of interest to know whether the decreased sucrose intake associated with extensive food and water deprivation (Forbes et al. 1996; Hatcher et al. 1996) is reversed by chronic treatment with antidepressant drugs. Returning to the CMS procedure, it is clear that the effects of CMS cannot be attributed simply to the food and/or water deprivation elements of the CMS procedure. This is because antidepressant-reversible effects on sucrose intake have been reported in studies using procedures in which there are no differences in food and/or water deprivation between the CMS and control groups (Griffiths et al. 1992; Muscat and Willner 1992, expts 6–9; Cheeta et al. 1994; Dauge et al. 1996; Smadja 1996; Bertrand et al. 1997; Valverde et al. 1997). Whatever the explanation of the effects reported by Forbes et al. (1996) and Hatcher et al. (1996), it does not apply to these studies.

While anhedonia appears the most likely explanation of CMS-induced decreases in sucrose/saccharin intake, it is clear from the above discussion that this conclusion cannot be drawn conclusively at present. However, the conclusion that CMS induces anhedonia is not based exclusively on data from experiments measuring responses to sweet tastes. Rather, this conclusion is based on convergent evidence from a variety of very different behavioural tests. In particular, deficits are apparent in reward paradigms that do not depend on consummatory behaviour. For example, CMS causes an increase in the threshold current required to support intracranial self-stimulation (brain stimulation reward) at electrodes implanted in the ventral tegmental area of the midbrain (Moreau et al. 1992, 1993, 1994a, b, 1995. As in the case of sucrose intake measures, the question has been raised whether the effects of CMS on brain stimulation reward threshold might be related to loss of body weight (Forbes et al. 1996); and as in the case of sucrose intake measures, their independence from body weight changes has been demonstrated (Willner et al. 1996). In addition to these effects on brain stimulation reward, CMS also attenuates or abolishes the ability to associate rewards with a distinctive environment (place conditioning). The latter effect has been demonstrated with a variety of different natural or drug reinforcers, but does not extend to aversive place conditioning; in the case of food-induced place conditioning, the effect of CMS is independent of food intake on the conditioning trials, which further argues against an involvement of nutritional factors in these effects (Papp et al. 1991, 1992; Muscat et al. 1992; Valverde et al. 1997).

To summarize, CMS causes a decrease in responsiveness to rewards in a variety of different behavioural paradigms (consumption of sweet diets; place conditioning with a variety of natural and drug rewards; brain stimulation reward threshold). While each of these behavioural changes is susceptible of a variety of interpretations, the most parsimonious account is that CMS causes a generalized decrease in sensitivity to rewards (anhedonia). The only serious challenge to this view arises from inferences drawn from the very extensive weight loss observed by the Aberdeen group (Matthews et al. 1995; Forbes et al. 1996), which is not replicated in data from many other laboratories, where decreases in sucrose drinking are apparent either in the absence of decreases in body weight, or after taking changes in body weight into account (Charkrabarti et al. 1996; Hatcher et al. 1996; Willner et al. 1996; Valverde et al. 1997: see also Griffiths et al. 1992).

Face validity

In addition to decreasing responsiveness to rewards, CMS also causes the appearance of many other symptoms of major depressive disorder. Behavioural changes in animals exposed to CMS include decreases in sexual (D'Aquila et al. 1994), aggressive (D'Aquila et al. 1994), and investigative (A. Barr, personal communication) behaviours, and decreases in locomotor activity. These are seen during the dark phase of the light-dark cycle, which is the rat's active period (Gorka et al. 1996); EEG measures of active waking are also decreased during the dark phase (Cheeta et al. 1997). In contrast, CMS did not cause the appearance of an "anxious" profile in two animal models of anxiety, the elevated plus-maze and the social interaction test (D'Aquila et al. 1994), suggesting that the behavioural changes are specific for depression. Animals exposed to CMS show an advanced phase shift of diurnal rhythms (Gorka et al. 1996), diurnal variation, with symptoms worst at the start of the dark (active) phase (D'Aquila et al. 1997), and a variety of sleep disorders characteristic of depression, including decreased rapid eye movement (REM) sleep latency, an increased number of REM sleep episodes, and more fragmented sleep patterns (Moreau et al. 1995; Cheeta et al. 1996). They also gain weight more slowly, leading to a relative loss of body weight (Muscat and Willner 1992; Willner et al. 1996), and show signs of increased activity in the hypothalamus-pituitary-adrenal (HPA) axis, including adrenal hypertrophy (Muscat and Willner 1992) and corticosterone hypersecretion (Ayensu et al. 1995). Abnormalities have also been detected in the immune system, including an increase in serum complement (Ayensu et al. 1995), decreases in thy-

Table 1 Symptom profile of the CMS model[a]

Depression	CMS
A. DSM-IV major depressive episode	
Duration	
At least 2 weeks	Effects of CMS persist for up to 3 months
Core symptoms	
Depressed mood	N/A
Markedly diminished interest/pleasure	Decreases in sexual and investigative behaviours decreased responses to rewards
Other symptoms	
Significant weight loss	Weight loss typically around 5%
Insomnia or hypersomnia	Disrupted sleep patterns
Psychomotor agitation or retardation	Decreased locomotor activity
Fatigue or loss of energy	Decreased "active waking" in EEG
Feelings of worthlessness or excessive or inappropriate guilt	N/A
Diminished ability to think or concentrate or indecisiveness	(Not tested)
Recurrent thoughts of death or suicide	N/A
B. DSM-IV melancholia	
Core symptom	
Loss of pleasure or lack of reactivity to pleasurable stimuli	Generalized decreased in responses to rewards
Other symptoms	
Distinct quality of depressed mood	N/A
Depression worst in morning	Effects worst at start of dark phase
Early morning awakening	Phase advance of diurnal rhythm of locomotor activity
Psychomotor agitation or retardation	Decreased locomotor activity
Significant anorexia or weight loss	Weight loss typically around 5%
Excessive or inappropriate guilt	N/A

[a] The left side of the table shows the symptoms required for a DSM-IV diagnosis of **A** major depressive episode and **B** major depressive episode with melancholic features; the right side of the table shows corresponding behavioural changes in rats exposed to CMS. Diagnosis **A** requires five or more symptoms including at least one core symptom; diagnosis **B** requires the core symptom and three or more other symptoms. N/A, not applicable: this is shown where the DSM-IV symptoms can only be known through the patient's verbal report. As the table refers specifically to DSM-IV, it excludes other characteristic features of depression that have also been reported in the CMS model, such as endocrine changes and decreased REM sleep latency. See text for references

mus weight, natural killer cell activity and reactivity to T-cell mitogens (Kubera et al. 1994, 1995), and an increase in acute phase proteins that was reversed by chronic antidepressant treatment (Sluzewska et al. 1996).

Taken together with the generalized decrease in responsiveness to rewards, these parallels to the symptoms of depression, and in particular, to melancholia, are both extensive and comprehensive (Table 1). Indeed, it is arguable that the only symptoms of depression that have not been demonstrated in animals exposed to CMS are those uniquely human symptoms that are only accessible to verbal enquiry (Willner 1991). There is certainly room in some cases for debate as to the extent to which the behaviours observable in rats correspond to the clinical symptoms: for example, psychomotor retardation is far more complex than a simple decrease in locomotor activity. Nevertheless, it is worth pointing out that, according to the diagnostic rules summarized in the legend to Table 1, a rat exposed to CMS could, in principle, legitimately attract a DSM-IV diagnosis of either major depressive disorder or major depressive disorder with melancholic features. (Whether in practice one would actually wish to make this diagnosis is another question!)

Predictive validity

The reversal of CMS-induced anhedonia typically requires 3–4 weeks of treatment, which closely resembles the clinical time course of antidepressant action; a second parallel with the clinic is that antidepressants act specifically in animals exposed to CMS, but do not alter rewarded behaviour in nonstressed control animals.

Studies have been conducted in the CMS model with a wide range of antidepressant and non-antidepressant agents, in addition to a number of putative novel antidepressants. Ineffective agents in the CMS model include chlordiazepoxide (Muscat et al. 1992), *d*-amphetamine (Papp et al. 1996), and the neuroleptics chlorprothixene, haloperidol (Papp et al. 1996) and risperidone (Moreau 1997); none of these drugs are effective as antidepressants. Also ineffective was the alpha-2 antagonist ethoxyidazoxan (Cheeta 1995), which appears to be ineffective as an antidepressant in the clinic, at least as monotherapy in unipolar depression (W. Potter, personal communication). Drugs shown to be effective in reversing CMS-induced anhedonia include the tricyclics imipramine, desipramine and amitriptyline (Willner et al. 1987; Muscat et al. 1990; Papp et al. 1996; Sluzewska and Szczawinska 1996a; Valverde et al. 1997), the SSRIs fluoxetine, fluvoxamine and citalopram (Muscat et al. 1992; Przegalinski et al. 1995; Marona-Lewicka and Nichols 1996; Sluzewska and Szczawinska 1996a, b), the specific NA reuptake inhibitor maprotiline (Muscat et al. 1992), the monoamine oxidase inhibitors moclobemide (Moreau et al. 1993) and brofaromine (Papp et al. 1996), and the atypical antidepressant mianserin (Cheeta et al. 1994; Moreau et al. 1994a). In all of these studies, antidepressants were ef-

fective at low to moderate doses (e.g. tricyclic doses of 5–10 mg/kg per day), and the full antidepressant response required, typically, 3–5 weeks of treatment. Other less conventional, but clinically effective, antidepressants that are also effective in the CMS model include the antimanic agents lithium (Sluzewska and Szczawinska 1996a) and carbamazepine (Sluzewsaka and Nowakowska 1994), and the 5-HT1A partial agonist buspirone (Przegalinski et al. 1995; Papp et al. 1996). Additionally, activity in the CMS model has been reported for the corticosterone synthesis inhibitor ketoconazole (Sluzewska and Nowakowska 1994), which has been reported to have clinical antidepressant activity in a recent open study (Thakore and Dinan 1995). Finally, electroconvulsive shock (ECS) has also been shown to restore normal responsiveness to reward in animals exposed to CMS, and unlike all of the drug effects listed above, this response was present after a single week of treatment (Moreau et al. 1995).

In addition to these clear and appropriate positive and negative responses, there are also a number of questionable findings. For example, morphine was effective early in treatment at a low dose (1 mg/kg), but the effects were not sustained (Smadja et al. 1995), and no activity was seen at a higher dose (an escalating regime rising from 10 to 90 mg/kg) (Papp et al. 1996); morphine has not been shown to be an effective antidepressant in properly conducted clinical trials, but was widely used for this purpose in the early part of this century (Willner 1985). Both mepyramine, an antihistamine, and atropine, an anticholinergic, showed antidepressant-like activity, and would appear to be false positives; however, it is not entirely clear that these drugs would not show clinical antidepressant activity if formally tested, and in the case of atropine, the argument that this drug might be antidepressant is quite compelling (Papp et al. 1996). Finally, unlike buspirone, the more specific $5HT_{1A}$ partial agonist ipsapirone was inactive in the CMS model; and this may represent a false negative response (Przegalinski et al. 1995). However, while ipsapirone has clear anxiolytic activity (Cutler et al. 1994), there are as yet no published studies claiming that ipsapirone is effective in major depressive disorder. Indeed, another $5HT_{1A}$ partial agonist, gepirone, has been reported to be an effective antidepressant in non-melancholic patients, but to be ineffective in melancholia, of which anhedonia is the core symptom (Amsterdam 1992). From these data, ipsapirone would not be predicted to reverse anhedonia.

To summarize, a wide variety of antidepressant drugs, as well as ECS, are active in increasing responsiveness to rewards in animals exposed to CMS (but not in control animals), and the time course of the therapeutic improvements closely mirrors the clinical action of these agents. Conversely, a number of non-antidepressants are inactive in the CMS model, as predicted. There are a few drugs that appear to behave in an inappropriate manner, but some of these apparent failures may reflect inadequacies in the clinical literature. At present, there are no unequivocal discrepancies between the model and the clinic (Table 2). This suggests that the CMS model provides a basis for drug development that could be used with a fair degree of confidence.

Table 2 Pharmacological profile of the CMS model[a]

	Hits	Misses
True	Tricyclics Imipramine Desipramine Amitriptyline	Anxiolytic Chlordiazepoxide
	SSRIs Fluoxetine Fluvoxamine Citalopram	Neuroleptics Haloperidol Chlorprothixene Risperidone
	NA uptake inhibitor Maprotiline	Psychostimulant Amphetamine
	MAO-A inhibitors Moclobemide Brofaromine	Opioid Morphine
	Atypical Mianserin	
	$5HT_{1A}$ agonist Buspirone	
	Electroconvulsive shock	
Probable	Corticosterone synthesis inhibitor Ketoconazole	$5HT_{1A}$ agonist Ipsapirone
	Anti-manic agents Lithium Carbamazepine	Alpha-2 antagonist Ethoxyidazoxan
Possible	Antihistamine Mepyramine	(None)
	Anticholinergic Atropine	
False	(None)	(None)

[a] The table shows the results obtained in the CMS model with pharmacological agents for which clinical data are available; experimental compounds tested in the model are not included. "Hits" are compounds that normalize behaviour in CMS-exposed animals; "misses" are compounds that fail to do so. "True" are compounds that are correctly classified; "false" are compounds that are incorrectly classified (none so far identified). References are given in the text

Reliability

Much of the literature on the CMS model derives from work carried out in the laboratory in which the procedure originated, and this raises the question of the extent to which the effects of CMS are replicable elsewhere. In fact, while there have been relatively few full-length publications from other laboratories, in recent years the CMS procedure has been quite widely adopted: some of the laboratories that have successfully established the procedure are listed in Table 3.

It has also become apparent that in addition to the laboratories listed in Table 3, there are also a number of laboratories in which the effects of CMS are less reliable, in

Table 3 Utilization of the CMS procedure

Prinicipal investigator	Location	Strain[a]	Reference[b]
Anisman[c]	Ottawa, Canada	C57BL/6J mice	Griffiths et al. (1992)
De Vry[c]	Cologne, Germany	Wistar	Smith et al. (1996)
Di Chiara[c]	Cagliari, Italy	Sprague-Dawley	G. Di Chiara, personal communication
Hagan[c,d]	Harlow, UK	Lister hooded	Birmingham et al. (1995a,b)
Moreau[c]	Basel, Switzerland	Wistar	Moreau et al. (1992, 1993, 1994)
Nichols	West Lafayette, USA	Sprague-Dawley	Marona-Lewicka and Nichols (1996)
Overstreet[c]	Chapel Hill, USA	Flinders sensitive	Pucilowski et al. (1993); Ayensu et al. (1995)
Papp	Krakow, Poland	Wistar	Papp and Moryl (1994, 1996)
Phillips[c]	Vancouver, Canada	Sprague-Dawley	A. Barr, personal communication
Reid[c,d]	Aberdeen, UK	Lister hooded	Matthews et al. (1995); Forbes et al. (1996)
Roques	Paris, France	Long-Evans	Bertrand et al. (1997); Valverde et al. (1997)
Sulser	Nashville, USA	Wistar	Charkrabarti et al. (1996)
Sluzewska	Lublin, Poland	Wistar	Sluzewska and Szczawinska (1996a,b)

[a] Except where stated, experiments were conducted in rats
[b] References are illustrative, not exhaustive
[c] These workers have provided Commentaries on this review
[d] The dispute between the Aberdeen/Harlow groups and other laboratories concerns the interpretation of CMS-induced decreases in sucrose drinking, rather than their reliability

the sense that the behavioural changes (e.g. decreases in sucrose drinking) are observed more sporadically, between or within experiments. Results of this type have been observed in the laboratories of J. Hagan, where CMS usually decreases but under some circumstances increases sucrose intake (Hatcher et al. 1996), C.K. Nielsen (Copenhagen: personal communication), where the procedure reliably decreases sucrose intake in mice but is less reliable in rats, and M.-H. Thiebot (Paris: personal communication). Somewhat disconcertingly, following a move from London to Swansea in 1993, the CMS procedure has worked rather erratically in our own laboratory: in addition to the typical long-lasting decrease in sucrose intake, we have also observed rapid habituation to the effect of CMS, some experiments have been ineffective, and we have sometimes seen increases in sucrose intake. Despite several attempts to understand the sources of the variability we have observed, this problem remains currently unresolved. However, there are a number of clues:

1. While the effectiveness of the CMS procedure does not appear to be confined to a particular strain of rat (see Table 3), it has been shown that sensitivity to CMS varies between strains (Griffiths et al. 1992; Pucilowski et al. 1993); therefore, a procedure effective in one strain might be only marginally effective in another.
2. Our geographical move coincided with an unavoidable change in our animal supplier. Just as there are strain differences in sensitivity to CMS, differences in sensitivity may also exist between rats of the same strain from different suppliers; such differences could arise either from genetic drift or from differences in rearing procedures. In both cases (strain and supplier), the effectiveness of CMS might be improved by increasing the overall stress intensity.
3. We have observed both strain and supplier differences in sensitivity to sucrose (see also Lush 1989): the 1% sucrose concentration that we have routinely used in PVG or Lister hooded rats is only marginally preferred to water in some batches of Wistar rats, leading to unstable patterns of consumption in repeated tests, even in control animals (Newton, D'Aquila and Willner, unpublished data); in light of this problem, we now use a 2% sucrose solution in Wistars, which produces more stable patterns of intake.
4. We have recently reported that there is diurnal variation in sensitivity to CMS, at least in Wistar rats, which, under our current procedures, show little or no response to CMS when tested during the light phase of the light-dark cycle, but show typical decreases in sucrose consumption and preference when tested at the start of the dark phase (D'Aquila et al. 1997).
5. The duration of single housing prior to the start of a CMS experiment may be important, with better results observed (informally) with a longer duration of single housing (M. Papp, personal communication). This factor could influence the intensity of social interaction occurring during CMS, which has been reported to be an important element of the CMS procedure (Muscat and Willner 1992).
6. In some experiments, weight loss may be a confound that masks the extent of CMS effects on sucrose intake. We have observed negative correlations between sucrose intake and body weight in animals subjected to CMS: the greater the weight loss, the smaller the suppression of sucrose intake (D'Aquila et al. 1997).
7. The possibility that different behavioural endpoints (e.g. sucrose intake versus intracranial self-stimulation threshold) may differ in their sensitivity to CMS merits investigation. Indeed, in some experiments we have seen impairments of place conditioning in animals that, by that stage of the experiment, had habituated to the effect of CMS on sucrose intake (D'Aquila and Willner, unpublished data).
8. CMS procedures differ in their details from laboratory to laboratory, largely in relation to convenience and logistics. However, while some standardization of the procedure may be desirable, there are no obvious factors that distinguish the laboratories in which the procedure operates reliably from those where it does not.

In view of these uncertainties, it is not possible to state at present what are the necessary and sufficient features of

the CMS procedure. However, there are some data indicating that the effect of variety within the CMS schedule is simply to prevent or delay habituation, which can occur rapidly when a single stressor is presented repeatedly (Griffiths et al. 1992; Muscat et al. 1992). Some studies have reported that reliable effects can be obtained with small sets of stressors (see Muscat et al. 1992): for example, one laboratory has reported a series of studies in Long-Evans rats using a combination of only three stressors, pairing, wet bedding and underfloor heating, each applied at night only, twice weekly (Smadja et al. 1995; Dauge et al. 1996; Smadja 1996; Bertrand et al. 1997; Valverde et al. 1997). In relation to the dispute discussed above concerning the significance of food deprivation within the overall CMS schedule, it should be noted that this procedure uses no food deprivation, other than the deprivation applied equally to CMS and control animals prior to each sucrose intake test.

As with many other behavioural procedures, laboratories wishing to establish the CMS procedure should not assume that their experiments will work optimally at the first attempt. However, the CMS procedure does operate reliably in a large number of independent laboratories (Table 3). Presumably, the factors responsible for variability of outcome will become clearer in due course.

Utility

It is beyond the scope of this paper to review in detail studies that have used the CMS procedure as an investigative tool. (Some of this material is reviewed in Willner and Papp 1997.) However, examples will be given of four types of investigation, in order to illustrate some potential applications.

1. A major function of animal models of depression is in antidepressant drug discovery. Drugs that appear antidepressant-like in the CSM procedure include the DA agonist pramipexole, which is currently in phase 3 clinical trials (Willner et al. 1994) and the COMT inhibitor tolcapone (Moreau et al. 1994b); the $5HT_{1A}$ agonist BIMT 17 (D'Aquila, Monleon et al., reported in Willner 1995a) and the 5HT releaser MMAI (Marona-Lewicka and Nichols 1996); and a variety of ligands acting as antagonists at different loci on the NMDA receptor complex (Papp and Moryl 1994, 1996). Ineffective agents include the enkephalinase inhibitor RB-101 (Smadja et al. 1995) and the CCK-B antagonist PD-134,308 (Smadja 1996). A particular application of a chronic model of depression is to investigate potential means of shortening the onset latency of antidepressant action. In the CMS model, acceleration of the onset of antidepresant action was achieved by co-administration, with a tricyclic or an SSRI, of either lithium or pindolol, both of which are claimed to show the same action in the clinic (Sluzewska and Szczawinska 1996a, b). Rapid onset has also been observed with the strychnine-insensitive-glycine-site partial agonist ACPC (Papp and Moryl 1996).

2. In addition to these studies of novel antidepressants, the CMS model has also been used to investigate the mechanism of action of conventional antidepressants. These studies have established that sensitization of D_2/D_3 receptors in the nucleus accumbens, following chronic antidepressant treatment, acts as a final common pathway for the anti-anhedonic actions of antidepressant drugs, irrespective of their primary mechanism of action (reviewed in Willner 1995b).

3. To the extent that the CMS procedure is valid as a model of depression, studies of the neurobiological substrates underlying the effects of CMS can provide insights into the pathophysiology of depression. For example, CMS causes antidepressant-reversible changes in the binding properties of a number of neuroreceptor systems, including decreases in D_2/D_3 receptors in the nucleus accumbens and increases in cortical beta-adrenergic and $5HT_2$ receptors. CMS also increased cortical $5HT_{1A}$ receptor binding, but this effect was not reversed by chronic antidepressant treatment (Papp et al. 1994a, b; reviewed in Willner and Papp 1997). A number of studies have reported post-mortem changes in neurotransmitter and metabolite levels (e.g. Willner et al. 1991); more interesting are recent studies using microdialysis to measure transmitter release in vivo. Initial results from this technique, in animals exposed to CMS, include decreases in DA release in nucleus accumbens (G. Di Chiara, personal communication) and prefrontal cortex (Smadja 1996), and a failure to respond to social stimulation with an increase of met-enkephalin release in the nucleus accumbens (Dauge et al. 1996).

4. Finally, it is important not to overlook the possibility that extrapolations from an animal model might increase insight into the nature of the disorder modelled. For example, we have confirmed predictions, derived from the effects of CMS in an operant paradigm (Cheeta 1995), that the induction of a depressed mood in human volunteers would increase cravings for chocolate (Willner et al. 1997) and cigarettes (Willner and Jones 1996). A second example arises from the fact that the very existence of the CMS model implies that a relationship between chronic mild stress and anhedonia should exist in depressed patients. As predicted, melancholic (anhedonic) patients scored significantly higher in their subjective perceptions of the severity of the minor stresses encountered in their daily lives, relative to both non-depressed controls and non-melancholic patients (Willner et al. 1990). Both of these findings are discussed further in the author's Response to the accompanying Commentaries.

Conclusions

In the 10 years since its first appearance (Willner et al. 1987), the CMS procedure has been extensively investigated, with encouraging results. In particular, considerable efforts have been made to evaluate the validity of the procedure as a model of depression. This review has summarized data pertinent to the performance of the

CMS model on the three dimensions of predictive validity, face validity and construct validity, and inter alia, has addressed criticisms of the model where they have arisen, particularly in relation to some aspects of construct validity. A conservative conclusion of this review is that the CMS model appears to be at least as sound as any other animal model of depression, and better than most. However, the procedure is not without problems. Foremost among these is the practical difficulty of carrying out CMS experiments, which are labour intensive, demanding of space, and of long duration. (On the other hand, the chronicity of the model also represents one of its major strengths, and was an important design objective.) Another significant drawback is that the procedure can be difficult to establish in a new laboratory, for reasons that need to be understood, but currently are not. However, it is abundantly clear that once established, as is now the case in many laboratories, the CMS model can be used to study problems that are extremely difficult to address by other means. Although the initial research with this procedure has been concerned primarily with the validity of the model, it is to be hoped that the next decade will focus increasingly on exploiting the potential of the CMS model, in its application to the study of depression and antidepressant drug action.

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