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ORIGINAL INVESTIGATION

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"Depression" increases "craving" for sweet rewards in animal and human models of depression and craving

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Abstract This study consisted of two experiments, one in rats and one in human volunteers, that used the identical progressive ratio (PR) operant procedure. In both experiments, responding was reinforced under a progressively increasing work requirement, and different groups of subjects received reinforcers that varied in sweetness. In experiment 1, rats were subjected to chronic mild stress, a well-validated animal model of depression. Performance under the PR schedule increased in subjects reinforced with conventional precision pellets (which contain 10% sucrose) or very sweet pellets, but not in subjects reinforced with sugar-free pellets. In experiment 2, volunteers were subjected to a depressive musical mood induction. Performance under the PR schedule increased in subjects reinforced with chocolate buttons, but not in subjects reinforced with with buttons made from the relatively unpalatable chocolate substitute carob. In experiment 2, depressive mood induction also increased chocolate craving, as measured by a novel questionnaire, and there were significant correlations between chocolate craving and chocolate-reinforced PR performance. These results suggest that performance under the PR schedule provides a measure of craving rather than reward, and that craving for sweet rewards is increased by depressive mood induction in both animal and human models. Implications for the interpretation of pharmacological studies using the PR procedure are also discussed.

Key words Depression · Musical mood induction · Chronic mild stress · Progressive ratio schedule · Sweet reward · Craving · Rat · Human volunteers

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Introduction

Although many animal models of depression are in current use (reviewed by Willner 1990), the majority of them have some major drawbacks, notably, a brief duration, the use of extreme conditions (e.g. severe electric shock), and a focus on aspects of behaviour of questionable relevance to the clinical condition (typically, changes in locomotor activity). In order to avoid each of these difficulties, the chronic mild stress (CMS) procedure was developed, which takes as the main target symptom anhedonia (a decreased pleasure capacity), which is the defining symptom of the melancholic subtype of major depression (Klein 1974; American Psychiatric Association 1994). In this model, chronic, sequential exposure, of rats or mice, to a variety of mild stressors causes a decrease in their responsiveness to rewards, which is typically monitored as a decrease in the consumption of dilute sucrose solutions, or a decreased preference for sucrose over water. This, and related effects may, under suitable conditions, be maintained over a period of weeks or months by continued application of the stress regime (Willner et al. 1987, 1992a; Willner and Papp 1997; Willner 1997).

CMS causes a range of other behavioural and physiological changes relevant to depression, in addition to the "core symptom" of the model (anhedonia): for example, CMS causes decreases in affective (eg. sexual) and locomotor behaviours (D'Aquila et al. 1994), and changes in the sleeping EEG characteristic of depression, such as a decrease in the latency to enter the first period of REM sleep (Cheeta et al. 1997). Indeed, all of the behavioural symptoms of major depressive disorder listed in DSM-IV have now been demonstrated in animals exposed to CMS, along with many of the biological markers characteristic of severe depressions (Willner et al. 1992a; Willner and Papp 1997). The relevance of this model to depression is further supported by evidence that the decreases in sensitivity to reward are reversed by chronic treatment with all of

the major classes of antidepressant drugs, and by electroconvulsive shock, but not by a variety of non-antidepressant drugs (Papp et al. 1996). Furthermore, the effects of antidepressants in this paradigm resemble the clinical situation, in two important respects: in both cases, treatment typically requires chronic (2–5 weeks) drug administration; and the effects are specific to the stressed/depressed state, since antidepressant treatment does not increase hedonic behaviour either in non-stressed control animals or in nondepressed human volunteers (reviewed by Willner et al. 1992a; Willner and Papp 1997).

Although the CMS paradigm has been extensively validated as a model of anhedonia, the primary behavioural measure, a decrease in consumption of palatable sweet fluids, is in principle open to a variety of other interpretations, which have been debated in the literature (reviewed by Willner 1997). On the whole, the evidence tends to support the interpretation that these effects reflect a decrease in responsiveness to sweet reward. However, it is clear that consummatory measures are less than ideal as indices of responsiveness to reward, and therefore a variety of other techniques have also been used to address this issue. In the place conditioning paradigm, animals display a preference for a distinctive environment in which they have previously received rewards (Carr et al. 1989); CMS attenuates or abolishes place preferences established using a variety of different reinforcers. By contrast, drug-induced place aversions were unaffected by CMS, indicating that the effects on place preference conditioning are unlikely to result from a nonspecific motivational impairment or a failure of associative learning (Willner et al. 1992a). CMS has also been shown to cause an increase in the threshold for brain stimulation reward (Moreau et al. 1992). Like the effects of CMS on sucrose intake, the effects on place conditioning (Valverde et al. 1997) and brain stimulation reward (Moreau et al. 1992) are also reversed by chronic antidepressant treatment.

The present studies were initiated in an attempt to provide further validation for the concept that CMS decreases responsiveness to rewards, using an operant procedure that is frequently employed to measure reward in the context of drug self administration research, the progressive ratio (PR) reinforcement schedule. In PR schedules, the work required to obtain successive reinforcers increases, up to a point (the breakpoint) at which subjects cease responding, and this point, measured either as the number of responses made, the number of reinforcers obtained, or the highest ratio completed, is taken as a measure of the efficacy of the reinforcer (Richardson and Roberts 1997). We therefore applied this methodology in rats exposed to CMS while performing under a PR schedule. Food pellets varying in sweetness were used, and it was predicted that CMS would decrease breakpoints, an effect that would increase in size with reinforcer sweetness. In the event, exactly the opposite results were obtained: far from decreasing performance, CMS increased breakpoints maintained by the sweeter pellets. This study constitutes experiment 1 of the present paper.

In order to understand better this perplexing effect, we decided to simulate the procedure as closely as possible in human subjects, in order to take advantage of the unique ability of human subjects to comment verbally on their behaviour. We have reported elsewhere that human voluteers performing the same PR schedule we had used in rats, but reinforced with puffs on a cigarette, produce performances very similar to those of rats (Willner et al. 1995), and that breakpoints in the PR schedule were increased in volunteers exposed concurrently to a depressive mood induction procedure (Willner and Jones 1996). This result resembles closely the effect of CMS in rats performing under a PR schedule maintained by sweet food pellets. In order to parallel the rat experiment more closely, we then repeated the experiment in volunteers reinforced with chocolate buttons: this study constitutes experiment 2 of the present paper. In addition to performing under the PR schedule following a depressive mood induction, subjects also reported on their mood state and their craving for chocolate, using, respectively, visual analogue mood scales (Bond and Lader 1974) and a novel chocolate craving questionnaire (Benton et al. 1997). We have previously reported that, in addition to increasing cigarette-reinforced PR performance, depressive mood induction also increased scores on a cigarette craving questionnaire (Willner and Jones 1996). We therefore predicted that induction of a depressed mood would similarly increase both chocolate-reinforced PR performance and scores on a chocolate craving questionnaire.

Materials and methods

Subjects

The subjects in experiment 1 were 54 male Lister hooded rats (Olac, Bicester), weighing approximately 300 g at the start of the experiment. They were singly housed under a 12-h light/dark cycle (lights on 0800 hours), with water freely available in the home cage. Tests were carried out between 1200 and 2000 hours. This experiment took place at London Guildhall University in 1992. The subjects in experiment 2 were 120 female volunteers (mean age 22.5 years), recruited from among the student population at University of Wales, Swansea, by means of posters asking for volunteers who liked chocolate. Subjects were not paid for participation, but those in the carob condition (see below) were given a chocolate bar (by way of compensation) at the end of the study.

Progressive ratio schedule

Both experiments used the same geometric PR schedule, under which the number of responses required doubled with each successive reinforcer, starting from an initial ratio of 1 for rats and 4 for human subjects. Subjects performing under these conditions

typically show a decelerating pattern of responding, which eventually ceases. The number of responses made up to the point at which responding ceased is known as the break-point, and is defined operationally as described below.

In experiment 1 (rats), the operandum was a lever in a conventional rat operant chamber (see below), and the reinforcers were 45 mg precision food pellets; the sucrose content of the pellets varied between experimental groups (see below). Pellets which were delivered to the rats in the conventional manner on completion of the ratio requirement. The session duration was 60 min, and the breakpoint was defined as the start of a response-free period of 300 s. As rats performing under this PR schedule of food reinforcement sometimes resume responding after meeting the breakpoint criterion (Cheeta et al. 1996), and also for comparability with the results of experiment 2, in addition to analyzing performance using this criterion, the data were subjected to two further analyses, using the total number of responses emitted during the 60-min session, and using a different breakpoint criterion, 120 s. In both cases, the results were very similar to those found using a 300-s breakpoint criterion; only the 300-s data are reported.

In experiment 2, subjects responded by pressing the space bar on a computer keyboard (IBM PC clone, programmed in Pascal). Responses made with an inter-response interval of < 250 ms were not recorded. Successful responses were acknowledged with a brief low-pitched tone, and reinforcer availability was signalled with a longer high-pitched tone. Details of the subject's performance were displayed to the experimenter on a monitor, which was positioned away from the subject's view. Reinforcers were chocolate buttons (sweet or bitter, in different experimental groups), which were handed to the subject by the experimenter for immediate consumption. In experiment 2 (human subjects), the breakpoint was defined as the start of a response-free period of 120 s, and the session terminated when this point was reached.

Questionnaires

The following instruments were used in experiment 2.

Mood scales

Mood was evaluated using the Bond and Lader (1974) visual analogue scales (VAS). Each scale consisted of a 100 mm horizontal line flanked by a pair of antonymous adjectives (e.g. alert – drowsy; happy – sad). Fifteen VAS were presented on a single page, with the negative pole to the left on eight scales and to the right on seven scales. Subjects were asked to mark each scale at a position that corresponded to their feelings at that moment; scales were scored by measuring the distance from the negative pole to the subject's mark. The means of scores on different scales provided scores on three factors, Alertness (nine scales), Contentedness (four scales) and Calmness (two scales).

Attitudes to chocolate

The Attitudes to Chocolate Questionnaire (Benton et al. 1997) consists of 24 scales, presented on two pages, in the form of statements (e.g. "I like to indulge in chocolate) followed by a 100 mm horizontal line labelled "not at all like me" on the left and "very much like me" on the right. Subjects were asked to mark each scale at a position that corresponded to their attitudes to chocolate at that moment; scales were scored by measuring the distance from the negative pole to the subject's mark. The mean of scores on different scales provided scores on three factors, Craving (e.g. "My desire for chocolate often seems overpowering": ten scales), Guilt (e.g. "After eating chocolate I often wish I hadn't": ten scales) and Functionality (eg. "I eat chocolate only when I'm hungry": four scales).

Impulsivity – venturesomeness – empathy (IVE)

The IVE questionnaire (Eysenck and Eysenck 1991) consists of 54 questions which subjects answer by circling "yes" or "no". Scores for Impulsivity (19 items), Venturesomeness (16 items) and Empathy (19 items) are obtained by summing appropriate positive or negative answers. This questionnaire was included in the study in order to investigate whether these personality factors influenced responses to the Attitudes to Chocolate Questionnaire.

Procedure: experiment 1

The rats were first trained by conventional methods to press a lever in one of nine identical single-lever operant chambers (Campden Instruments, Loughborough), under conditions of 6-h food deprivation; a force of approximately 9 g was required to depress the levers. Each animal was always tested in the same chamber. Each chamber was controlled by a BBC microcomputer programmed in BBC basic. All animals were trained using 45 mg precision pellets as the reinforcer, but the sucrose content of the pellets varied. The animals were allocated to three groups ($n = 18$), which were trained using pellets containing 1%, 10% (standard) or 95% sucrose, respectively. Each animal received the same pellet type throughout the study. A stimulus light positioned above the food hopper was illuminated for 0.5 s as each pellet was delivered.

Following the acquisition of lever pressing, the animals were maintained on 6-h food deprivation and received 27 daily 5-min sessions, during which every lever press was reinforced (continuous reinforcement: CRF). Subsequently, the animals were transferred to the PR schedule, and 25, 60-min sessions were conducted under these conditions. For the next 12 sessions, the PR schedule continued in operation, but deprivations conditions alternated from day to day between 23-h deprivation and no deprivation.

Subsequently, the animals from each pellet type group were subdivided into two groups ($n = 9$), one of which was subjected to a modified version of the CMS procedure; food deprivation was not used as a stressor, as both control and stressed animals were food deprived prior to some of the operant testing sessions. A variety of mild stressors made up the CMS procedure, which in each week consisted of two periods (7-h and 20-h) of water deprivation, two periods of continuous overnight illumination; one 8-h period of 45° cage tilt; two 15-h periods of confinement in a small (mouse) cage ($33 \times 15 \times 13$ cm); one 20-h period of paired housing, one 15-h period in a soiled cage (100 ml water in sawdust bedding; and two 5-h periods of low intensity stroboscopic illumination (300 flashes/min).

During the CMS phase of the experiment, performance under the PR schedule was tested under conditions of 23-h food deprivation on days 3, 7, 14 and 21 of CMS, and without food deprivation on days 4, 8, 15 and 22. The means of the final two sessions under conditions of 23-h and 0-h deprivation were used as baseline measures.

Procedure: experiment 2

Subjects attended the laboratory on a single occasion and were tested individually. No specific instructions were given regarding eating prior to the session, but time of last meal was recorded. Menstrual state was also recorded, as increases in chocolate craving in the premenstrual period have been reported (Bancroft et al. 1988; Rozin et al. 1991).

Subjects first completed the IVE questionnaire, the VAS mood scales and the Attitudes to Chocolate Questionnaire. Subjects were then allocated randomly to two groups ($n = 60$), and listened to through headphones to music intended to induce either elated or depressed moods (Clark 1983). This procedure was used in

preference to a verbal mood induction procedure, because musical mood induction is more effective and places fewer attentional demands on the subject (Clark 1983). Subjects in the Depressed condition listened to an extract from Prokoviev's Alexander Nevsky (Russia under the Mongol Yoke), played at half speed; subjects in the Elated condition listened to an extract from Delibes' Coppelia. Subjects were instructed to concentrate on the mood and to try to experience the mood suggested by it. At the end of 3 min, subjects completed the VAS mood scales and the Attitudes to Chocolate Questionnaire for a second time.

It was then explained to the subjects that chocolate buttons could be earned by pressing the space bar on a computer keyboard, and the tones signalling successful responses and reinforcer availability were demonstrated. The progressive nature of the task was not explained, but subjects were told that they could stop and restart responding at any time, and that a break in responding of 2 min would terminate the session. At this stage, each group of subjects was further randomly divided into two subgroups ($n = 30$), who were reinforced either with milk chocolate buttons or with carob buttons of approximately the same size.

After completing the PR task, subjects completed the VAS mood scales and the Attitudes to Chocolate Questionnaire for a third time. Finally, subjects allocated to the Depression condition were given a set of Elation inducing statements (Williams 1984), and asked to read them, concentrating on the mood suggested by the statements, until restored to a normal mood (Frost and Green 1982).

Data analysis

The effects of CMS (experiment 1) and mood induction (experiment 2) were analyzed by analysis of variance, supplemented by tests of simple main effects using the appropriate analysis of variance error term (Winer 1971). Breakpoint data from experiment 1 were analyzed using a four-factor analysis, with between-subjects factors of pellet type (1%, 10% and 95% sucrose) and stress (CMS or control), and within-subjects factors of deprivation level (23-h or no deprivation) and successive tests (baseline and four tests during CMS). In experiment 2, each factor of the VAS mood scales and the Attitudes to Chocolate questionnaire was subjected to three-way analyses, with between-subjects factors of mood (elated or depressed) and reinforcer (sweet or bitter chocolate), and the within-subjects factor of successive tests. PR data (responses to breakpoint and number of reinforcers earned) were analyzed by two-way between-subjects analyses.

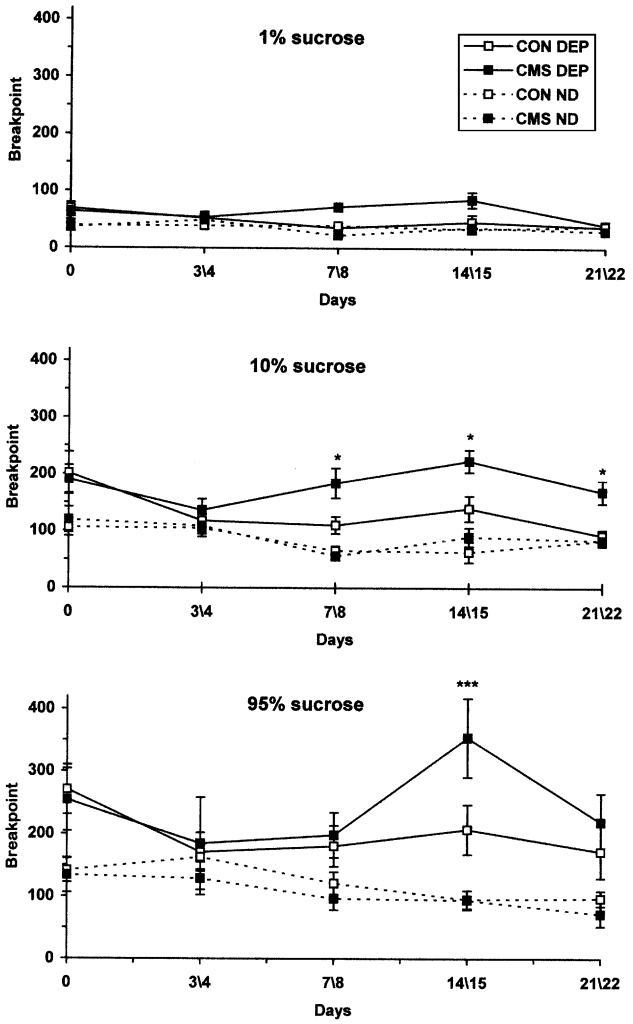

Fig. 1 Effects of CMS on breakpoint in the progressive ratio schedule in rats. Different groups of rats ($n = 9$) were reinforced with 1% (*top*), 10% (*middle*) or 95% (*bottom*) sucrose pellets. Different rats underwent CMS or control (*CON*) treatments, and all rats were tested under conditions of no deprivation (ND) on the first day of each pair of test days, and following 23-h food deprivation (*DEP*) on day 2 of each pair of test days. $*P < 0.05$, $***P < 0.001$, relative to control animals tested with food deprivation. Values are means ± SE

Results

Experiment 1

Performance of rats under the PR schedule is shown in Fig. 1. Breakpoints increased as a function of reinforcer sweetness [$F(2,48) = 35.1$, $P < 0.001$] and were higher when animals were tested following a period of food deprivation [$F(1,48) = 92.9$, $P < 0.001$]. The main effect of stress was not significant [$F(1,48) = 1.6$, NS], but there were significant two and three-way interactions of stress with deprivation [$F(1,48) = 8.8$, $P < 0.005$], weeks [$F(4,192) = 10.3$, $P < 0.001$], and deprivation × weeks [$F(4,192) = 3.4$, $P < 0.01$]. There were also significant two- and three-way interactions of reinforcer sweetness with deprivation [$F(2,48) = 14.3$, $P < 0.001$] and deprivation × weeks [$F(8,192) = 2.5$, $P < 0.02$].

Further analysis showed that none of the simple main effects or interactions involving stress was significant in non-deprived animals. Therefore, all subsequent analysis was carried out on data from deprived animals only. In deprived animals, analysis of simple main effects showed significant effects of stress [$F(1,48) = 6.5$, $P < 0.025$] and interactions of stress with weeks [$F(4,384) = 6.0$, $P < 0.001$] and reinforcer sweetness with weeks [$F(8,384) = 2.3$, $P < 0.05$]. Stress appeared to increase responding in deprived animals reinforced by 1% sucrose pellets, but these effects were not significant (Fig. 1, top panel). However, in deprived animals reinforced by 10% or 95% sucrose pellets, breakpoints were increased in stressed animals, relative to controls. In animals reinforced by 10%

sucrose pellets, there was a significant overall effect of stress [$F(1,48) = 4.2$, $P < 0.05$], which arose from significant increases in breakpoint after 7, 14 and 21 days of stress (Fig. 1, middle panel), while in animals reinforced by 95% sucrose pellets there was a significant stress × weeks interaction [$F(4,384) = 5.5$, $P < 0.001$], reflecting a significant increase in breakpoint after 14 days of stress (Fig. 1, bottom panel).

Experiment 2

Subject characteristics

Subjects reinforced with chocolate in the PR procedure were slightly older than those reinforced with carob [means: 21.3 versus 23.78, $F(1,116) = 4.2$, $P < 0.05$]. None of the other variables recorded prior to mood induction (time of last meal; premenstrual state; personality scales; mood factors; attitudes to chocolate) varied significantly as a function of reinforcer type, mood induction procedure, or their interaction [all $P > 0.1$].

Personality, mood and attitudes to chocolate

The relationship between personality and mood measures and attitudes to chocolate was examined using data from the first administration of the Attitudes to Chocolate Questionnaire, which was completed prior to mood induction. Among the three factors of this questionnaire, Functionality was positively correlated with Craving ($r = 0.35$, $P < 0.001$) and negatively correlated with Guilt ($r = -0.29$, $P < 0.001$); the relationship between Craving and Guilt was nonsignificant ($r = 0.11$).

Table 1 shows the relationships between personality and mood measures on the one hand, and attitudes to chocolate on the other. Guilt was inversely related to Venturesomeness ($P < 0.01$), Alertness ($P < 0.02$), Calmness ($P < 0.001$) and Contentedness ($P < 0.001$). The only other significant relationship was between Functionality and Venturesomeness ($r = 0.22$, $P < 0.02$), but this relationship was nonsignificant when calculated as a partial correlation, controlling for Guilt ($r = 0.16$). With this very minor exception, neither personality (as measured by the IVE) nor mood state had any influence on chocolate Craving and Functionality, prior to mood induction.

Table 1 Personality, mood, and attitudes to chocolate[a]

	Craving	Functionality	Guilt
Impulsivity	0.04	0.12	−0.07
Venturesomeness	−0.05	0.22*	−0.24**
Empathy	0.05	0.04	0.16
Alertness	−0.02	0.13	−0.22*
Calmness	−0.01	0.15	−0.36***
Contentedness	−0.10	0.14	−0.24***

[a] *$P < 0.02$, **$P < 0.01$, ***$P < 0.001$

Effects of mood induction on mood state

As predicted, exposure to the mood induction procedures caused significant mood changes. On the Contentedness factor (Fig. 2), there was a significant Mood × Tests interaction [$F(2,232) = 24.4$, $P < 0.001$]. There were no significant effects involving Food type (all F-values < 1). Further analysis, using tests of simple main effects, showed that the Elated and Depressed groups did not differ significantly prior to mood induction [$F(1,116) = 0.5$, NS], but did differ significantly after mood induction [$F(1,116) = 27.6$, $P < 0.001$]; this effect was still present, though somewhat attenuated, at the end of the experiment [$F(1,116) = 6.0$, $P < 0.025$]. The difference between the groups resulted from a substantial decrease in Contentedness in the Depressed group [$F(2,232) = 33.9$, $P < 0.001$], with no significant changes in the Elated group [$F(2,232) = 1.5$, NS].

A similar pattern of effects was seen on the Alertness factor (results not shown). In this case, the significant Mood × Tests interaction [$F(2,232) = 27.7$, $P < 0.001$] resulted from a small increase in Alertness in the Elated group [$F(2,232) = 6.3$, $P < 0.01$], together with a substantial decrease in Alertness in the Depressed group [$F(2,232) = 30.4$, $P < 0.001$]. In the case of Calmness, both the main effect of Mood and the Mood × Tests interaction were nonsignificant [$F(1,116) = 1.4$; $F(2,232) = 1.2$, respectively]. The only significant effect in this analysis was a small decrease in Calmness over successive Tests [$F(2,232) = 3.2$, $P < 0.05$].

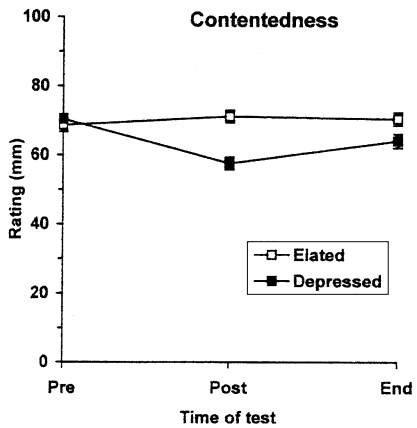

Fig. 2 Visual analogue scale ratings of Contentedness before (*Pre*), and immediately after (*Post*) the induction of depressed (■) or elated (□) mood states, and at the end of the experiment. Values are means ± SE

Effects of mood induction on attitudes to chocolate

Mood induction had no significant effects on either Functionality or Guilt ($P > 0.1$, NS, for all main effects and interactions: results not shown). However, mood induction did influence Craving, which increased following the induction of a depressed mood (Fig. 3). Both the main effect of mood state [$F(1,116) = 4.0$, $P < 0.05$] and the mood × time interaction [$F(2,232) = 5.8$, $P < 0.005$] were significant. Analysis of simple main effects showed that the two groups did not differ significantly before mood induction, but did differ significantly both immediately following mood induction and at the end of the experiment [$F(1,116) = 6.2$, 4.6, respectively, $P < 0.05$]. This reflects the fact that there was no significant change over tests in the Elated group [$F(2, 232) = 1.1$, NS], but a significant increase in Craving in the Depressed group [$F(2,232) = 6.0$, $P < 0.01$].

Effects of mood induction on PR performance

The effects of depressive mood induction on PR performance are summarized in Fig. 4. For both measures of PR performance (responses to breakpoint and number of reinforcers earned), there was a significant Mood × Reinforcer interaction [responses: $F(1,116) = 11.3$, $P < 0.001$; reinforcers: $F(1,116) = 8.3$, $P < 0.005$]. For both measures, Mood had no effect on PR performance maintained by the carob reinforcer ($F < 1$), but significantly increased PR performance maintained by the sweet chocolate reinforcer [responses: $F(1,116) = 18.8$, $P < 0.001$; reinforcers: $F(1,116) = 4.8$, $P < 0.05$].

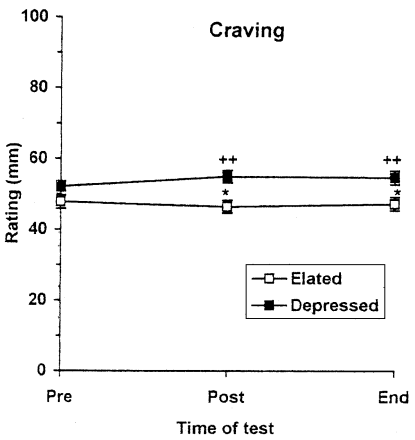

Fig. 3 Questionnaire-derived ratings of chocolate craving before (*Pre*), and immediately after (*Post*) the induction of depressed (■) or elated (□) mood states, and at the end of the experiment. $^{*}P < 0.05$ for difference between groups; $^{++}P < 0.01$ for difference from Pre baseline. Values are means ± SE

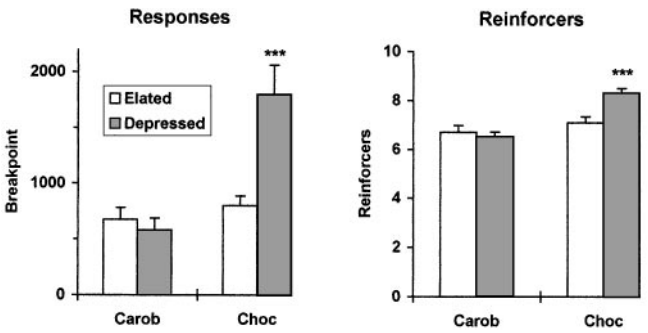

Fig. 4 Performance of human volunteers in the progressive ratio schedule reinforced by carob or chocolate, and after induction of depressed (■) or elated (□) mood states ($n = 30$). Values are means ± SE of responses emitted (*left*) or reinforcers earned (*right*) before reaching the breakpoint. $^{***}P < 0.001$ relative to elated group

PR performance as a measure of chocolate craving

In order to evaluate the relationship between PR performance and the questionnaire measure of chocolate craving, correlations were computed, within each of the two Reinforcer type subgroups ($n = 60$), between behavioural measures and the second administration of the Attitudes to Chocolate questionnaire, which followed mood induction and immediately preceded the PR task. In the Carob group, correlations between behavioural and questionnaire measures were close to zero (max $r = 0.1$). However, in the Chocolate group, both Craving ($r = 0.37$, $P < 0.005$) and Functionality ($r = 0.28$, $P < 0.05$) were significantly correlated with the number of responses made. In order to control for mood effects, these analyses were repeated while partialling out both the effect of Mood induction, and current mood, as represented by Contentedness, Alertness and Calmness scores on the second (post-MIP) administration of the mood VAS; age and the three measures from the IVE were also partialled out. The correlations between each of the questionnaire measures and responses to breakpoint remained significant after taking all of these factors into account ($r = 0.31$, $P < 0.025$ for both Craving and Functionality].

Discussion

Progressive ratio performance in animal and human depression models

CMS increased breakpoints for rats performing under a PR schedule, but only in acutely food-deprived animals, and only with sweet pellets (experiment 1). These results were unexpected on the basis of previous work. Many studies have demonstrated that CMS decreases the consumption of weak sucrose solutions, at sucrose concentrations of around 0.5–2% (reviewed by Willner

et al. 1992a; Willner 1997). This effect is not seen at higher sucrose concentrations, and indeed, under some circumstances, CMS many increase consumption of a very sweet diet (Willner et al. 1991; Sampson et al. 1992). At first sight, these effects may appear similar to those observed in the present study. However, they are not. Consumption of sucrose solutions by rats shows a curvilinear relationship to concentration, such that at low sucrose concentrations, an increase in concentration results in an increase in consumption, while at higher concentrations, a further increase in concentration leads to a decrease in consumption. Similar effects are seen in rats performing under continuous reinforcement maintained by food pellets varying in their sucrose concentration, or consuming a sweetened wet mash: at very high sucrose concentrations, intake decreases (Phillips et al. 1991a,b; Sampson et al. 1992; Cheeta et al. 1995). The cause of this decrease in intake of very sweet diets is unclear. However, the development of an aversive component can be excluded (for sucrose, though not for saccharin), because in choice tests, rats greatly prefer the sweeter of two solutions, even though this may be relatively under-consumed in a single-bottle test (Muscat et al. 1991; Phillips et al. 1991b). That is, it appears that a sweeter sucrose solution is more rewarding than a less-sweet solution, irrespective of the level of intake of each, and a decrease in sweetness decreases reward across the whole range of sucrose concentrations. In consumption tests, CMS decreases intake at low sucrose concentrations but may increase intake at high concentrations, and both of these effects are closely comparable to those of a decrease in sweetness. We have therefore argued that this similarity between the effects of CMS and those of a decrease in sweetness imply that, like a decrease in sweetness, CMS decreases the rewarding properties of sucrose across the whole concentration range (Willner et al. 1991, 1992a; Sampson et al. 1992). However, the effects of CMS in the present study do not resemble those of a decrease in sucrose concentration. Under the PR schedule, the breakpoint increases monotonically as the sweetness of the pellets increases. (This may be seen in Fig. 1, for example, at day 0; cf. also Cheeta et al. 1995.) In other words, under these conditions, CMS and a decrease in sweetness have opposite effects: respectively, an increase and a decrease in the breakpoint. Therefore, the effects of CMS in the present study cannot be interpreted as a decrease in the rewarding properties of sucrose. We return below to the question of developing an alternative interpretation of these data.

In an attempt to understand the discrepancy between the predicted results (CMS decreases breakpoint) and those observed (CMS increases breakpoint), we initiated a series of studies in which the same PR schedule that we had used in rats was implemented in human subjects. In the initial studies, the subjects were smokers, and performance was reinforced by puffs on a cigarette. Induction of a depressed mood, using the musical mood induction procedure, caused an increase in breakpoint, comparable to that observed in rats maintained on a PR schedule of sweet reinforcement (Willner et al. 1995; Willner and Jones 1996). The present data (experiment 2) are compatible with our earlier human PR data, in showing that depressive mood induction increased performance in subjects maintained on a PR schedule of sweet reinforcement. These data are also fully consistent with the rat data (experiment 1), in showing that depressive mood induction increased performance maintained by sweet reinforcement, but did not increase performance maintained by non-sweet reinforcement.

Additional information derived from the human model

Other than the nature of the depression model (CMS in rats versus depressive mood induction in volunteers), the major difference between the two experiments was the use in human subjects of a questionnaire to evaluate their subjective cravings for chocolate. This questionnaire was developed in a previous study, using factor analysis to extract three factors, labelled Craving, Guilt and Functionality (Benton et al. 1997). Although there are significant intercorrelations between these factors, they behave differently with respect to other variables. For example, Guilt was negatively associated with positive mood states and with the personality variable Venturesomeness (present data), Functionality correlates with performance in a glucose tolerance test (Donohoe 1997), and Craving is associated with the eating of chocolate bars (Benton et al. 1997). Questions loading on the Craving factor of the Attitudes to Chocolate Questionnaire fall into two groups. Firstly chocolate is a source of some distraction; it is "overpowering", "preys on my mind", you cannot "take it or leave it" and "can't get it out of my head". The second group of questions associated the craving dimension reflect a weakness for chocolate when under emotional stress; it is eaten "when I am bored", "to cheer me up", "when I am upset" and "when I am down" (Benton et al. 1997). The coupling of these two groups of questions suggests a link between negative mood and an intense desire to consume chocolate. The present data demonstrate that induction of a depressed mood increased subjects' reports of the intensity of their craving for chocolate. This effect was specific for the Craving dimension: Guilt and Functionality were unaffected by the mood induction procedure.

The effect of depressive mood induction to increase chocolate craving is consistent with the clinical literature. For example, Schuman et al. (1987) found that a group who reported "self-medicating with chocolate" were more likely to have personality traits associated with hysteroid dysphoria, a syndrome characterized by

episodes of depression in response to feeling rejected. The experience of strong food cravings is associated with being more bored, anxious and having a dysphoric mood (Hill et al. 1991; Hill and Heaton-Brown 1994). Desires for chocolate are associated with depression (MacDiarmid and Hetherington 1995), but not related to suicidal thoughts (Lester and Bernard 1991). Thus, there is considerable evidence that food-cravings in general, and chocolate-craving in particular, are associated with mood disturbance. However, in contrast to most previous research, the present study has not examined subjects chosen because of their abnormal eating patterns or psychiatric complaints. The finding of an association between chocolate craving and mood state in the present study demonstrates that this relationship exists in the normal population, and confirms a causal role of depressed mood in increasing chocolate craving.

These findings provide important insight into the interpretation of the behavioural data. In previous studies, we have reported that performance in a PR schedule maintained by cigarette reinforcement was significantly correlated with a questionnaire measure of cigarette craving (Willner et al. 1995), and that depressive mood induction increased both of these measures (Willner and Jones 1996). In the present study, depressive mood induction similarly increased both chocolate craving and breakpoint in the PR schedule maintained by sweet reinforcement, and again, there was a significant correlation between these two measures. The correlation between chocolate craving and PR performance was independent of mood, since it was maintained when the effects of mood induction and mood state were controlled statistically. This suggests that when sweet chocolate is used as the reinforcer, performance in the PR schedule provides a measure of chocolate craving.

Depressive mood induction did not increase breakpoint in the PR schedule maintained by the less palatable carob reinforcer, but in this case there was no significant correlation between craving and performance. It is possible that these differences between chocolate and carob may reflect the relatively greater familiarity of chocolate, and the greater likelihood that chocolate may have been consumed during previous episodes of depression (Hill and Heaton-Brown 1994; MacDiarmid and Hetherington 1995). However, almost all subjects in the carob group commented in debriefing that they had disliked the taste, most having assumed that they had been eating chocolate that was of poor quality or very old.

It is important to note that the increases in chocolate craving and chocolate-reinforced PR performance occurred in circumstances in which a decrease would be expected in subjects' liking for chocolate. We have previously shown that depressive mood induction causes a decrease in subjective reports of pleasure capacity, as measured by the Fawcett-Clark Pleasure Capacity Scale (Willner and Healy 1994), which is accompanied by a decrease in the perceived pleasantness of taste stimuli: the published data report a decrease in the perceived pleasantness of cheese (Willner and Healy 1994), and we have also observed a decrease in the perceived pleasantness of chocolate following depressive mood induction (Willner and Netherton, unpublished). This means that the increase in PR performance following depressive mood induction is consistent with, and correlated with, the increase in chocolate craving (increased), but does not reflect changes in liking for chocolate (not measured in this experiment, but on the basis of earlier data, probably decreased).

Interpretation of the effects of CMS on PR performance

These results provide a basis for interpreting the effects of CMS in experiment 1. In rats performing under the PR schedule, we had predicted a decrease in breakpoint, but in the event, we observed either no change or an increases in breakpoint. Similar results have recently been reported by Phillips and Barr (1997), who saw no change in PR performance following CMS; but the same animals did show the typical reduction in sucrose intake (which was not tested in the present study). However, the prediction of a decrease in breakpoint is based on the assumption that the breakpoint in a PR schedule provides a measure of the rewarding properties of the reinforcer. The human studies suggest a different interpretation: in the case of a sweet reinforcer, the breakpoint provides a measure of craving, rather than reward. If the PR paradigm provides a model of craving, then there are no grounds for predicting a decrease in breakpoint in animals exposed to CMS. Indeed, on the basis of the human volunteer studies, in which a depressive mood induction elicited increases in craving for cigarettes (Willner and Jones 1996) and chocolate (present data), the prediction should be that, if anything, CMS, in rats, should cause an increase in breakpoint. This is exactly what was observed. Furthermore, craving in human volunteers was unrelated to PR performance maintained by a non-sweet reinforcer, and induction of a depressed mood failed to alter this performance. This may indicate that the effect of depressive mood induction to increase PR performance is only observable under high incentive conditions, which may explain the lack of effect of CMS in animals tested with the sugar-free reinforcer, or in the absence of prior food deprivation.

The suggestion that performance in a PR schedule may provide a measure of craving is not new. PR performance is most frequently used in drug self-administration studies, and has been proposed as a model of drug craving in this context (Markou et al. 1993). However, PR performance is more usually considered

to represent a measure of the rewarding properties, or reinforcing efficacy, of a self-administered drug (e.g. Richardson and Roberts 1997), and there is typically no basis for distinguishing between these two interpretations. In drug self-administration studies, for example, at doses below those that elicit motor impairments, breakpoint increases as the dose per infusion increases, and this could be interpreted equally well as either an increase in the rewarding properties of the higher dose (Richardson and Roberts 1997), or a greater craving for the higher dose (Markou et al. 1993). The same is true, under control conditions, of performance maintained by food pellets varying in sweetness.

However, the CMS paradigm dissociates these two interpretations. In this paradigm, the rewarding properties of sucrose decrease, as indicated by tests of sucrose consumption, sucrose preference (see Willner et al. 1992a; Willner 1997), or sucrose-induced place conditioning (Papp et al. 1991), but PR performance increases (present study). The human studies suggest strongly that this increase in PR performance should be interpreted as an increase in craving, which co-exists alongside a decrease in reward. CMS has been shown in place conditioning studies to decrease the rewarding properties of amphetamine and morphine (Papp et al. 1991, 1992; Valverde et al. 1997). On the basis of the present data and other studies in human volunteers (see above), an increase in breakpoint, reflecting an increase in craving, would be predicted in the PR performance of animals exposed to CMS while self-administering psychostimulants or opiates.

It is interesting to note that in this study we have used a set of human models to resolve a problem arising in the context of animal models, and having no obvious means of solution in that context. This is the exact inverse of the usual strategy, in which animal models are used to address issues in human behaviour that cannot be approached directly in human subjects. Since problems in the interpretation of animal models abound, it is worthwhile to consider whether human models might find wider application for this purpose. Much of the debate around the applicability of animal models relates to their degree of homology with the human behaviour they purport to represent. As discussed in a recent symposium, the development of testing procedures that closely align human behaviour to the procedures used in other species can greatly facilitate the extrapolations between species that form the basis of many of the inferences drawn from animal models (Robbins 1996; Sagvolden 1996; Swerdlow 1996; Willner 1996).

Implications for the interpretation of pharmacological studies using the PR procedure

There is strong evidence that the anhedonic effects of CMS are mediated by a decrease in transmission at dopamine D_2/D_3 receptors in the nucleus accumbens. For example, CMS has been shown to attenuate behavioural responses to D_2/D_3 receptor agonists, and to decrease the density of D_2/D_3 receptors in this region, an effect reversed by chronic treatment with imipramine (Willner et al. 1991; Papp et al. 1994). This evidence is complemented by a substantial literature demonstrating that neuroleptic drugs, which are D_2/D_3 receptor antagonists, block rewarded behaviour, in a manner that parallels the effects of CMS: for example, neuroleptics increase the brain stimulation reward thresholds (Stellar and Rice 1989), and decrease sucrose intake and preference (Muscat and Willner 1989; Phillips et al. 1991b); and the decrease in preference for sweet rewards is seen following drug administration within the nucleus accumbens (Phillips et al. 1991c). CMS and neuroleptic drugs also have similar effects in relation to very sweet rewards. As noted above, at high concentrations of sucrose in the diet, consumption falls, relative to less sweet diets, and under these conditions, CMS fails to suppress and may enhance consumption. Similarly, consumption of very sweet fluids (Phillips et al. 1991b) or food (Sampson et al. 1992), is enhanced by neuroleptics. As discussed above, all of these effects are interpretable as reflecting a decrease in the hedonic impact of sweet rewards.

However, CMS and neuroleptic treatment differ in their effects on PR performance. As demonstrated in the present study, CMS increased breakpoint in the PR schedule. However, we have reported previously that the specific D_2/D_3 receptor antagonist raclopride caused a dose-dependent decrease in breakpoint (Cheeta et al. 1995). How is this discrepancy to be explained? Although neuroleptics do decrease reward (see above), this property may not be responsible for their effects on PR performance. Neuroleptics are also known to cause a time-dependent decrease in operant responding, which appears gradually during the course of the session (see, e.g. Willner et al. 1992b; Sanger and Perrault 1995). The behavioural processes that give rise to these response decrements are poorly understood (see Willner et al. 1992b), but they arise within the dorsal striatum, rather than the nucleus accumbens (Phillips et al. 1991c; Beninger and Ranaldi 1993), and so appear distinct from the anhedonic effect of neuroleptic drugs. Performance in a PR schedule is defined by the breakpoint, which, by definition, occurs at the end of the session, and any treatment that selectively suppresses behaviour at the end of the session would have the effect of decreasing breakpoint. In other words, the effect of neuroleptic drugs on PR performance must inevitably be confounded with the time-dependent, response-decremental effect of these drugs. We conclude that the apparent discrepancy between the effects of CMS and those of raclopride, on PR performance maintained by sweet reward, may arise because the apparent effect of raclopride in this

paradigm is artefactual. This conclusion is supported by the results of a recent study in which the breakpoint of animals performing under a PR schedule of food reinforcement was increased by dopamine-depleting 6-OH-DA lesions within the nucleus accumbens (Bowman et al. 1997). This effect is opposite to that observed with raclopride (Cheeta et al. 1995), but consistent with the effect of CMS (experiment 1). The fact that a paradoxical increase in PR performance is seen following both CMS and 6-OH-DA lesions of the nucleus accumbens is consistent with the hypothesis (see above) that the effects of CMS on rewarded behaviour are mediated by a decrease in DA function within this structure.

This analysis, that the effects of neuroleptic drugs on PR performance may to some extent be artefactual, has important implications for the interpretation of studies that have used the PR paradigm to evaluate the effects of neuroleptic treatment on drug self-administration. Consistent with the effect of raclopride on a PR schedule reinforced by sweet food (Cheeta et al. 1995), neuroleptic drugs also decrease the breakpoint of animals performing PR schedules of cocaine self-administration. These effects have been interpreted as evidence that dopamine receptor blockade decreases the reinforcing efficacy of cocaine (or cocaine craving, depending on one's theoretical standpoint: Markou et al. 1993; Richardson and Roberts 1997). However, while typical neuroleptics, such as spiroperidol, haloperidol or flupenthixol, decrease breakpoints in animals self-administering cocaine under a PR schedule (Hubner and Moreton 1991; Richardson et al. 1994), the atypical neuroleptic clozapine, which does not elicit a time-dependent response decrement (Sanger and Perrault 1995), actually increases the breakpoint (Loh et al. 1992). As the neuroleptic-induced response decrement appears to arise within the dorsal striatum (Phillips et al. 1991c; Beninger and Ranaldi 1993), the absence of this effect may reflect the selectivity of clozapine for the mesolimbic dopamine system (White and Wang 1983). This effect of clozapine to increase PR performance maintained by cocaine resembles the effect of CMS, observed in the present study, on PR performance maintained by sweet reward. As the effect of clozapine is uncontaminated by the response-decrement artefact, the increase in breakpoint observed with clozapine, in PR performance maintained by cocaine self-administration, may provide the more accurate reflection of the effect on PR performance of blocking dopamine transmission within the nucleus accumbens.

Conclusions

The PR paradigm measures the willingness of subjects, animal or human, to work for rewards, which, in this procedure, are infrequently received. This measure of reward-seeking behaviour correlates, in human subjects, with cravings for both cigarettes and chocolate. Reward seeking behaviour is conceptually distinct from the response to a reward when it is presented, which is evaluated by, for example, preference or intake tests in animals, and by liking ratings in human subjects. This distinction between appetitive and consummatory aspects of rewarded behaviour has a long and distinguished intellectual pedigree (e.g. Konorski 1967; Bindra 1968; Bolles 1972; Stein 1983; Klein 1987). It would be reasonable to expect that these two dimensions would usually go hand in hand: that is, that more valued rewards would be more highly craved, or that unwanted rewards would be little valued. However, experience teaches that wanting and liking are frequently not in balance. Indeed, this concept forms the centrepiece of certain theories of drug addiction (Robinson and Berridge, 1993; Di Chiara 1997). While not necessarily subscribing to or endorsing these theories, the present data represent an empirical demonstration that "wanting" and "liking" can indeed be dissociated: the imposition of CMS in rats or the induction of a depressed mood state in human volunteers both cause a general decrease in responsiveness to rewards (Willner and Healy, 1994; Willner 1997), including a decrease in responsiveness to sweet rewards (Willner 1997; Willner and Netherton, unpublished data), yet in both cases, the same procedures increased reward-seeking behaviour, which in human subjects correlates with subjective reports of cravings.

To summarize, we predicted that exposure of rats to CMS, an animal model of depression, would decrease the breakpoint of animals performing under a PR schedule of reinforcement. What we in fact observed was that, rather than decreasing breakpoints, both CMS in rats and induction of a depressed mood in a human model increased PR performance maintained by sweet reinforcement. This apparent paradox is potentially resolved by the evidence from human studies that PR performance does not provide a measure of reward, our original assumption, but rather, a measure of craving. This conclusion, and a further consideration of the apparent discrepancy between the effects of CMS and of neuroleptic drug treatment in the PR paradigm, lead us to suggest that the effects of typical neuroleptic drugs in this paradigm may be artefactual, and that these effects may have been misinterpreted in the drug self-administration literature. We note, finally, that this use of human models to resolve problems of interpretation in animal models is an unusual strategy that merits wider evaluation.

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