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Review article

Vocalizations during withdrawal from opiates and cocaine: possible expressions of affective distress

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Abstract

Intense anxiety has been postulated to trigger relapse to abuse of opiates and psychomotor stimulants. Preclinical research methodologies need to be developed to adequately characterize the affective or emotional component of withdrawal. Classically, withdrawal from psychomotor stimulants and opiates focuses on somatic and autonomic indices, foremost based on observational assessments and, additionally, on measures of disrupted conditioned behavior. These measures depict the intensity and time course of withdrawal from specific doses of opiates and psychomotor stimulants, but require large numbers of subjects due to single use of each individual. Behavioral disruptions have been attributed to anhedonia, a core symptom of drug withdrawal, as well as major depressive and psychotic disorders. In spite of some pharmacological validation, inferences about anxiety-like disturbances, based on observed somatic and autonomic signs or on changes in conditioned responses, have to remain tentative. High-pitched vocalizations may communicate affective expressions and, in rodents, different kinds of ultrasonic vocalizations communicate maternal separation distress in infants, accompany the intensely arousing phases of agonistic confrontations, signal submission and distress in defensive responses to threats and painful events, and are part of the excitatory and inhibitory phases of sexual behavior. While acute treatment with opiates, psychomotor stimulants, alcohol and benzodiazepines suppresses ultrasonic vocalizations in the 22–25-kHz range, rats emit high rates of ultrasonic vocalizations upon withdrawal from prolonged exposure to these drugs, particularly if they have been startled. Peak rates of ultrasonic distress calls occur ca. 1–3 days after cessation of cocaine or opiate treatment and decline within 5–7 days. Ultrasonic vocalizations during withdrawal from cocaine, alcohol or benzodiazepines can be attenuated by renewed access to the drug. It will be informative to learn how the neural circuit mediating vocalizations interacts with the ones subserving self-administration of alcohol, opiates and psychomotor stimulants.

Keywords: Opiate; Opioid; Cocaine; Amphetamine; Withdrawal; Benzodiazepine; Alcohol; Vocalization; Ultrasound; Distress

1. Introduction

The term ‘‘anxiety’’ refers to distress and uneasiness in common parlance and, in psychiatric definitions of anxiety disorders, the excessive and recurrent nature is highlighted such as in panic, phobias, obsessive-compulsive, post-traumatic distress and generalized anxiety disorders (Barlow and Wincze, 1998). The focus on anxiety in drug abuse is chiefly related to its postulated role in instigating relapse to intensive alcohol, opiate and stimulant abuse following periods of abstinence (Kosten et al., 1986; Markou et al., 1998; Satel et al., 1991). In an influential scheme of the addiction cycle, Gawin and Kleber (1986) have pointed to signs and symptoms of anxiety and craving in the phase of withdrawal from cocaine that is most significant in promoting relapse.

Most drugs of abuse may induce transient positive states such as feelings of well-being or euphoria that contrast profoundly with dysphoric states during withdrawal from the drug. The Opponent Process Theory has been used in order to account for these contrasting effects of drugs at different stages of the self-administration cycle (Ettenberg et al., 1999; Solomon, 1980). While initially euphoric effects may reinforce drug taking positively, alleviation of a per-

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sistent negative affective state and physiological distress during withdrawal appears to negatively reinforce continued drug taking. Operationally, such renewed drug taking is defined as being negatively reinforced, that is discontinuation or removal of aversive anxiety-like and depressive-like symptoms as well as other physiological symptoms of distress are the key consequences for continued drug self-administration (Ahmed et al., 2002; Jaffe, 1985; Markou and Koob, 1991). Although there is no universal consensus for defining dependence adequately, quantifiable withdrawal symptoms following discontinuation of drug taking can be accepted as sufficient evidence (Jaffe, 1992), and they represent the cardinal criteria for diagnosing substance dependence according to the Diagnostic and Statistical Manual of Mental Disorders (4th edition; American Psychiatric Association, 1994). While discontinued use of drugs such as alcohol and opiates produces clear signs of withdrawal including tremors, nausea, tachycardia, seizures and fever, as well as affective and psychosomatic disturbances such as craving, anxiety and depression, psychomotor stimulants do not produce such clear signs of dependence (Farrell, 1994; Lago and Kosten, 1994). Still, 12–60 h after discontinuing a binge of psychomotor stimulant use, symptoms comprising motivational fatigue, decreased psychological well-being—often referred to as anhedonia, and dysphoria concurrently develop with intense emotional memories about the cocaine euphoria (Gawin, 1991). These symptoms of affective distress, in conjunction with severe craving, have been viewed as significant determinants for relapse to cocaine binges.

The most likely time for resuming drug use, including stimulants, opiates and alcohol, corresponds to the point at which anxiety is reportedly at its highest peak after cessation of drug taking (Gawin, 1991). A challenge for preclinical research remains the need to more adequately characterize the affective or emotional component of withdrawal. Classic experimental models in animals have relied on disruption or suppression of ongoing behavioral performance or exaggeration of reflexive responses for the study of drugs with anxiolytic potential (Brady, 1956; Davis and Gallager, 1988; Geller and Seifter, 1960). Inferences about the cause for disrupted or exaggerated behavior remain, however, tentative and indirect due to the multiple causes for these types of behavioral changes. Similarly, the term ‘‘anxiety’’ in clinical populations is merely a hypothetical construct used to describe more than one possible disruption of the behavioral repertoire. Preclinical studies of affective distress have begun to delineate the underlying mesocorticolimbic circuits that offer targets for pharmacotherapeutic interventions (Burgdorf et al., 2001; Miczek et al., 1991, 1995; Stutzmann et al., 1998; Vivian and Miczek, 1999).

The current review will initially discuss long-established indices of drug withdrawal, foremost based on observational assessments and, additionally, on measures of disrupted conditioned behavior during withdrawal from psychomotor stimulants and opiates. The final section will focus on a methodological approach that promises to capture the affective dimension of drug withdrawal states, namely distress vocalizations.

2. Preclinical assessment of withdrawal from psychomotor stimulants

Stimulant use originates during intermittent episodes of controlled drug taking that are scrupulously regulated by the user. Dependence is established following the transition to prolonged periods of uncontrollable drug taking that occur during recurrent binges that may last in excess of 24 h (Gawin, 1989). The prevailing consequences of this intense form of stimulant use are characterized by substantial disturbances in mood and behavior amid periods of abstinence. Unlike opiates and alcohol, stimulants do not produce readily identified physiological and behavioral signs of withdrawal upon cessation of the typical binge. The psychological features of cocaine addiction have been summarized by Gawin (1991). A protracted dysphoric syndrome induces continued cocaine use, and this syndrome includes anxiety, lack of motivation, boredom and low activity with diminished experiences of pleasure (anhedonia). This syndrome begins to appear within 12 h after the crash. In this state of anhedonia, memories of euphoria during previous cocaine binges induce severe cravings and prompt renewed use.

This characterization de-emphasizes the classical signs of physical dependence (i.e., overt somatic signs) as the hallmark features of substance abuse (Jaffe, 1985; Redmond and Krystal, 1984). An alternative proposal is that substance dependence arises from distinct neural adaptations within mesocorticolimbic circuitry that contribute to the quality of emotional experiences, including the sensation of pleasure (Henry et al., 1998; Koob et al., 1997; Kuczenski et al., 1991; Terwilliger et al., 1991). In agreement with this hypothesis, only a limited number of somatic withdrawal signs are detectable after discontinuing binge patterns of stimulant administration in preclinical assessments. A continued challenge for preclinical experimental protocols is to target and capture the behavioral expression of affective states that are significant to stimulant drug taking, and the negative affect associated with withdrawal (Barros and Miczek, 1996; Kantak and Miczek, 1988; Pliakas et al., 2001). Several methodologies for measuring unconditioned and conditioned behavior have been employed to evaluate ‘‘anxiety-like states’’ expressed during withdrawal from stimulants.

2.1. Observational studies

One type of experimental strategy for assessing anxiety-like behavior relies on the observation of behavioral responses without an explicit conditioning history. Exam-

ples are behaviors in such commonly used tasks as the "open field," "elevated plus maze" or "social interaction test" (File et al., 1982; Lister, 1987; Whimbey and Denenberg, 1967). These tasks arrange environmental conditions such as bright light and unfamiliarity that suppress exploratory or social behavior, and this suppression or inhibition is hypothesized to be due to fear and anxiety. The profile of hypothalamic–pituitary–adrenal activity establishes these tasks as stressful, and drugs with clinically established anxiolytic efficacy are detected with few 'false positives' and 'misses' (Pellow et al., 1985; Rodgers, 1997). Observational assessments are relatively simple to conduct, although they necessitate the use of many experimental subjects, given the large individual variations, and their use is limited due to rapid habituation. The reliance on the initial reaction to an unfamiliar, aversive environment points to the assessment of a state of anxiety rather than a trait.

So far, the effects of stimulant withdrawal on measures of suppressed exploratory behavior have been relatively inconsistent. For example, Sarnyai et al. (1995) demonstrated that exploration of the elevated plus-maze is significantly impaired during withdrawal from systemically administered cocaine (20 mg/kg, i.p., once daily, for 14 days). In contrast, other reports have found that exploratory behavior is not influenced by cocaine withdrawal at similar time intervals and following similar administration regimens (Basso et al., 1999; Lilly and Tietz, 2000). Withdrawal from cocaine (1.0 mg/kg, b.i.d., for 14 days) suppresses social interactions severely, and suppressed social behavior during stimulant withdrawal has been reversed with serotonergic drugs such as ondansetron (Costall et al., 1990). However, impaired exploratory behavior in the plus maze during cocaine withdrawal does not appear to be reversible by serotonergic anxiolytics such as buspirone (Paine et al., 2002). These tests require many subjects, with single use of a matched pair of socially interacting animals or a single animal at a specific time point precluding an assessment of the course of withdrawal in a particular individual.

2.2. Disruption of conditioned performance

Withdrawal from repeated or continuous administrations of cocaine and amphetamine results in large, quantifiable changes in conditioned behavior, controlled by several schedules of reinforcement and discriminative stimuli. A decline in the rates of conditioned responses that are maintained by various schedules of reinforcement is the most apparent consequence of withdrawal from stimulants (Kleven and Woolverton, 1991). After long periods of administering systemic injections of amphetamine (1.5 mg/kg/day, for 27 days) or continuous infusions of cocaine (32 mg/kg/day, for 65 days), tolerance and withdrawal can be observed (Campbell and Seiden, 1973; Woolverton and Kleven, 1988). Tolerance to the disruption of operant performance during chronic stimulant administration may be related to the progressive increases in stimulant seeking and taking behavior. It is not clear, however, how disrupted operant performance during withdrawal is directly related to affective distress.

Responding maintained by a progressive ratio schedule of sucrose reinforcement shows a lowering of the breakpoint during the first 3 days of withdrawal from chronic amphetamine, using an escalating dose protocol (Leith and Barrett, 1976) that delivers increasing doses of amphetamine (1–10 mg/kg, three times per day over 4 days) (Barr and Phillips, 1999). These results are interpreted to reflect a "motivational deficit" for natural reward that is engendered during the early phase of withdrawal from amphetamine. This hypothesis was corroborated in an additional study demonstrating that selective motivational components of male sexual behavior in rats are also attenuated after cessation of a similar amphetamine injection regimen (Barr et al., 1999).

Of particular relevance are studies investigating intracranial self-stimulation (ICSS) thresholds, since this method attempts to characterize more quantitatively the affective dimensions of stimulant withdrawal (Kokkinidis et al., 1980; Kokkinidis and Zacharko, 1980; Markou et al., 1992). Shortly after the termination of chronic amphetamine administrations (<10 mg/kg/day, over 14 days), a significant increase in the current intensity is required to maintain intracranial self-stimulation responding and this threshold-elevating effect is interpreted as a depression of reward processes during withdrawal (Leith and Barrett, 1980). The increase of intracranial self-stimulation threshold after the termination of stimulant self-administration is immediate, but becomes apparent most significantly after 24–72 h of withdrawal and begins to subside within 2 weeks (Markou and Koob, 1991).

Several interpretations for a disruption in responding for schedule-controlled conditioned behavior during stimulant withdrawal have been postulated, and perhaps the most prominent is the one attributing the behavioral disruption to anhedonia, a core symptom of drug withdrawal, as well as major depressive and psychotic disorders. In interpreting the significance of disrupted or suppressed conditioned responses or elevated intracranial self-stimulation thresholds, it is important to exclude disturbances in sensory, motor and motivational activity during withdrawal from stimulants as the major determinants. Most prominent are the confounding physiological effects of stimulant withdrawal, including motor deficits, lethargy and anergia, simply because the effects of withdrawal from stimulants are characteristically in direct opposition to psychomotor stimulation (Gawin and Ellinwood, 1988). Stimulant-induced anorexia may influence schedule-controlled behavior that is maintained by alimentary reinforcers, although stimulant-induced changes in secondary reinforcement appear more relevant than those in primary reinforcement (Hill, 1970). However, these issues have been carefully

examined and apparently do not contribute to the behavioral suppression and on intracranial self-stimulation thresholds during withdrawal (Barr et al., 1999; Caul et al., 1988; Markou and Koob, 1992).

Pentylenetetrazol is a convulsant drug that can exert anxiogenic effects at subconvulsant doses and it acts primarily on γ-aminobutyric acid-A ($GABA_A$) receptors via blockade of the chloride ion channel (Allan and Harris, 1986). The interoceptive discriminative cue for pentylenetetrazol can be substituted for several drug withdrawal states ranging from stimulants to benzodiazepines (Jung et al., 2002). For example, rats trained to discriminate saline from pentylenetetrazol will choose the pentylenetetrazol-appropriate lever when undergoing withdrawal from psychomotor stimulants (Wood and Lal, 1987). The duration of stimulant exposure directly influences the amount of pentylenetetrazol-appropriate responding (Wood et al., 1989). Cessation of cocaine administrations (20 mg/kg, every 8 h) given over 14 days generated more pentylenetetrazol-appropriate responding (90%) than when given only for 3 consecutive days (<40%). The effects of stimulant withdrawal on pentylenetetrazol-appropriate responding are prevented by diazepam (20 mg/kg). Interestingly, the acute administration of cocaine at higher doses is frequently reported to produce anxiogenic effects and high doses of cocaine have been shown to substitute for pentylenetetrazol during drug discrimination trials, whereas low doses of cocaine do not (Wood and Lal, 1987). A limitation of interpreting drug discrimination studies is the uncertainty as to the precise nature of the interoceptive stimulus. Highly distressing experiences such as social defeat in an aggressive confrontation generalize to the pentylenetetrazol cue (Vellucci et al., 1988; Vivian et al., 1994b) supporting the interpretation of a fear- or anxiety-like state.

3. Preclinical assessment of opiate withdrawal

A major hypothesis attributes a key role to the experience of anxiety during withdrawal from opiates in the relapse to opiate seeking and taking (Goldstein, 1972). Behavioral, somatic and autonomic signs of opiate withdrawal can be identified across many organisms, ranging from invertebrates to humans, and are characterized by a distinctive onset, time-course and intensity. Typically, physiological and behavioral signs of withdrawal from opiates include responses that are opposite to those of the drug's acute effects (e.g., sedation vs. hyperactivity, hypo- vs. hyperthermia, euphoria vs. dysphoria, etc.) in support of the opponent-process theory (Weiss et al., 2001). Multiple behavioral responses emerge following cessation from opiate administration that have been interpreted to reflect an anxiety-like withdrawal state (Redmond and Krystal, 1984) and some of these behavioral indices of withdrawal are described below.

3.1. Observational studies

The most common method for quantifying and assessing the nature of withdrawal from opiates has been by observing and checking or counting, specific behavioral and physiological signs (Marshall and Weinstock, 1971; Wei et al., 1973a). For instance, administration of high doses of opiates to most rodents decreases motoric activities (i.e., walking, rearing and jumping) that are increased during withdrawal in a dose-dependent manner beyond the level of placebo-treated animals (Bläsig et al., 1973). In a detailed summary of observable signs during withdrawal from opiates, Bläsig et al. (1973) characterized the manifestation of several behavioral withdrawal signs in the rat, and delineated their time course of occurrence during early and late stages of dependence. Despite the consistency of clearly observable behavioral signs during withdrawal from opiates, alternative interpretations concerning the expression of particular behaviors that are not associated with anxiety-like states are possible. For example, opiate withdrawal has variable effects on core body temperature (Martin et al., 1963; Schwartz et al., 1978). The manifestation and intensity of particular withdrawal behaviors, including the archetypical wet-dog shakes and jumping, are readily apparent when the environmental temperature is either cold (<10 °C) or hot (>34 °C), respectively (Wei et al., 1973b). These types of withdrawal behaviors can be engendered by manipulating solely the ambient temperature and may represent more accurately a specific response to physiological challenges (Hainsworth, 1967; Wei et al., 1973a) rather than anxiety-like responses. Observational studies reveal clear dose- and time-dependent behavioral and physiological changes that characterize the magnitude and duration of opioid withdrawal, but they do not capture directly the affective dimension of withdrawal.

3.2. Disruption of conditioned performance

Performance of conditioned behavior under the control of schedules of reinforcement has proven to serve as a sensitive measure for examining quantitatively and qualitatively the effects of opiate administration, before and during the development of tolerance and during withdrawal (McMillan, 1973). Before the development of tolerance, opiates typically have multiphasic effects on the rate of operant responding maintained by most schedules of reinforcement in the rat (Brady and Holtzman, 1980; Ford and Balster, 1976; Thompson et al., 1970; Young and Thompson, 1979). For example, low doses of morphine (between 1.8 and 5.6 mg/kg) increase rates of positively reinforced responding and higher doses (10–30 mg/kg) usually decrease responding in rats (Brady and Holtzman, 1980). The development of tolerance is indicated by a significant rightward shift in the dose–response curve to morphine and this effect is seen using several routes of morphine administration, as well as in several species, including rats, mice, pigeons and non-

human primates (DeRossett and Holtzman, 1985; Jensen and Thompson, 1982; Miczek and Winslow, 1987; Negus et al., 1993).

Withdrawal from morphine in dependent animals produces a clear biphasic effect on rates of operant responding (Ford and Balster, 1976; Schulteis et al., 1997). During early protracted or precipitated withdrawal from morphine (i.e., <24 h), rates of conditioned responding are significantly suppressed (Brady and Holtzman, 1980; Goldberg and Schuster, 1967). The suppression of operant responding by precipitated withdrawal, using selective opioid receptor antagonists, can be engendered following as few as one or two opioid receptor agonist administrations (Meyer and Sparber, 1977; Schulteis et al., 1997). The reduction in operant responding during early withdrawal coincides with unambiguous somatic signs of dependence, including wet dog shakes, diarrhea, ptosis and weight loss (Schulteis et al., 1994; Wei et al., 1973b). The degree of dependence appears to be determined by the frequency and intensity of opiate administration, and acute dependence has been attributed to the presence of somatic signs of withdrawal following as few as only one opiate administration (Heishman et al., 1989). After ca. 2 days of opiate withdrawal, rates of operant responding increase significantly above original baseline levels before returning to baseline within 5–10 days (Ford and Balster, 1976). This extended period of change in operant responding during opiate withdrawal corresponds to an increase in "general excitability" that is also reflected by a considerable increase in unconditioned locomotor activity (Lorenzetti and Sancilio, 1970). It appears that the initial effects on operant performance can be precipitated for more than half a year after the administration of opiates, similar to other persistent responses to opiates, including physiological changes (Glick and Cox, 1977; Martin et al., 1963). Rates of operant responding before and after the onset of opiate withdrawal produce a reliable source of information about the time course of withdrawal, however, whether or not a transient disruption and subsequent increase in conditioned operant performance reflect disturbances in specific receptor-mediated neural adaptations, motoric capacities, complex motivational processes or anxiety-like responses, during opiate withdrawal, remains to be determined.

4. Distress vocalizations

During intense excitement, humans emit high-pitched sounds (Ploog, 1988; Williams and Stevens, 1981) and high-frequency vocalizations appear to be related to highly frightening as well as attraction behavior in other mammals (Bentley et al., 2000; Jürgens, 1983; Tembrock, 1975). In addition to communicating affective expressions, vocalizations may also serve semantic, pragmatic and physiologic functions, which may complement the expression of emotion (Scherer and Zei, 1988).

In myomorphic rodents, different types of vocalizations extend from the part of the spectrum that is audible for humans to the ultrasonic range (Sales and Pye, 1974). Infant mice and rats emit calls in the ultrasonic range (35 and 56 kHz, respectively) when separated from the dam and littermates and exposed to an ambient temperature that is lower than that prevalent in their nest (Fish et al., 2000; Hofer, 1996). These calls are part of the maternal separation response in the first 2 weeks postpartum. In adult mice and rats, male copulatory behavior is accompanied by very high-frequency short ultrasonic calls before ejaculation and the lower-frequency and longer ultrasonic post-ejaculatory "song" (Barfield et al., 1979; Barfield and Geyer, 1972, 1975; Nyby and Whitney, 1978; White et al., 1998). Adult rats also emit several types of vocalizations during aggressive confrontations with short high-frequency ultrasonic calls (ca. 56 kHz) by the aggressor and long lower-frequency ultrasonic calls accompanying defensive and submissive responses (Thomas et al., 1983; van der Poel and Miczek, 1991). The latter type of calls in the 22–25-kHz range are also detectable when a rat reacts to a noxious, painful or a startling stimulus (Miczek et al., 1991). It appears that ultrasonic distress vocalizations are more readily emitted in the presence of a receiving audience, giving support to the hypothesis that these calls communicate distress with the objective of altering the receiver's behavior.

Pharmacological studies of ultrasonic vocalizations have mostly focused on the reduction of calls by infant animals during maternal separation distress and on adult animals exposed to threats by an aggressive opponent or to electric foot shocks (Brudzynski and Eckersdorf, 1988; DeVry et al., 1993; Gardner, 1985; Miczek et al., 1995; Olivier et al., 1998; Panksepp et al., 1978b; Winslow and Insel, 1991). A selective reduction in the rate of ultrasonic vocalizations by stressed infant, or adult, rats and mice as a result of opioidergic, GABAergic or serotonergic treatments continues to be interpreted as predictive of the drugs' anxiolytic potential (Fish et al., 2000; Rowlett et al., 2001; Vivian et al., 1997; Vivian and Miczek, 1993a). For example, the decrease in murine ultrasonic vocalizations by 5-hydroxytryptamine-1B (5-HT_{1B}) receptor agonists in the absence of impaired motor activity and compromised thermoregulation points to specific anxiolytic-like effects of these agents which contrast with the reductions by positive modulators of $GABA_A$ receptors that are part of more pervasive sedative effects (Fish et al., 2000).

While acute administration of opiates, positive modulators of the $GABA_A$ receptors, catecholaminergic and serotonergic drugs *reduce* the rate of ultrasonic vocalizations in infant and adult rodents that are exposed to several social and environmental stressors with varying degrees of specificity, rodents emit ultrasonic vocalizations at significantly higher rates when subjected to withdrawal from opiates, benzodiazepines and also cocaine (Barros and Miczek, 1996; Miczek and Vivian, 1993; Mutschler and Miczek, 1998a,b; Vivian

and Miczek, 1991). These divergent changes in the rate of ultrasonic vocalizations after acute drug administration versus withdrawal are consonant with the predictions of the Opponent Process Theory of drug abuse (Koob and Le Moal, 2001).

4.1. Distress vocalizations during cocaine withdrawal

Rats emit ultrasonic vocalizations when withdrawing from self-administered cocaine, particularly when prompted by mild startling stimuli (Mutschler and Miczek, 1998a,b), and this response appears consistent with the emotional distress described clinically (Lago and Kosten, 1994). An initial demonstration involved rats drinking a cocaine solution using a two-bottle choice procedure. Discontinuation of limited 4 h daily access for 30 or 60 days, or continuous access for 30 days, led to a significantly increased emission of ultrasonic distress vocalizations when the rats were startled by mild tactile stimuli (Barros and Miczek, 1996). The rate of ultrasonic distress calls peaked after 3 days of withdrawal from consuming the cocaine solutions and the elevated rate of vocalizations persisted for as long as 28 days. These findings were interpreted to represent anxiety-like responses that were dissociated from the motoric hyperactivity as reflected by the startle reflex and disturbed thermoregulation. Oral intake of cocaine solution produces modest circulating blood and brain levels of cocaine, and the amounts vary considerably from day to day, producing no observable signs of withdrawal upon discontinuation. Even given these limitations, the animals emit high rates of ultrasonic vocalizations upon challenge with a mild startling stimulus, although the exact amount of consumed cocaine is not directly related to the magnitude and rate of the ultrasonic distress calls.

Intravenous cocaine self-administration procedures allow for precise control over the dose that is administered by the experimental subject and cocaine deliveries occur with precisely specified behavioral contingencies, namely upon fulfilling a behavioral demand. An experimental protocol with particular relevance to the human condition is the study of intravenous cocaine self-administration over the course of prolonged periods of unlimited access, referred to as *binges* (Covington and Miczek, 2001; Markou and Koob, 1991; Tornatzky and Miczek, 2000). Binges in preclinical intravenous self-administration models disclose patterns of responding for cocaine infusions that incorporate a shift from regulated to "out-of-control" drug taking, as seen in compulsive cocaine users (Goldstein, 1994). As early as 6 h after cessation of a 48-h binge in rats, cocaine self-administering rats emit significantly more ultrasounds in response to a mild tactile stimulus (i.e., 0.7 kg/cm^2 air puff) as compared to their yoked saline controls, and anxiety-like vocalizations are particularly strong and frequent at 24 h after a binge (Mutschler and Miczek, 1998a; see Fig. 1).

The amount of cocaine accumulated during binges of 48 h or more varies among individual rats due to the self-imposed cessation of self-administration after ca. 17–20 h of access, leading to a varied magnitude of the withdrawal vocalizations (Mutschler and Miczek, 1998a; Tornatzky and Miczek, 2000). When the experimental cocaine binge is limited to 16 h in order to reduce the variability in cumulative intake (Mutschler and Miczek, 1998a,b; Mutschler et al., 2000), the rates of ultrasonic vocalizations emitted in response to mild tactile stimuli peak at 24 h after a 16-h binge and remain significantly elevated for at least 5 days thereafter (see Fig. 2).

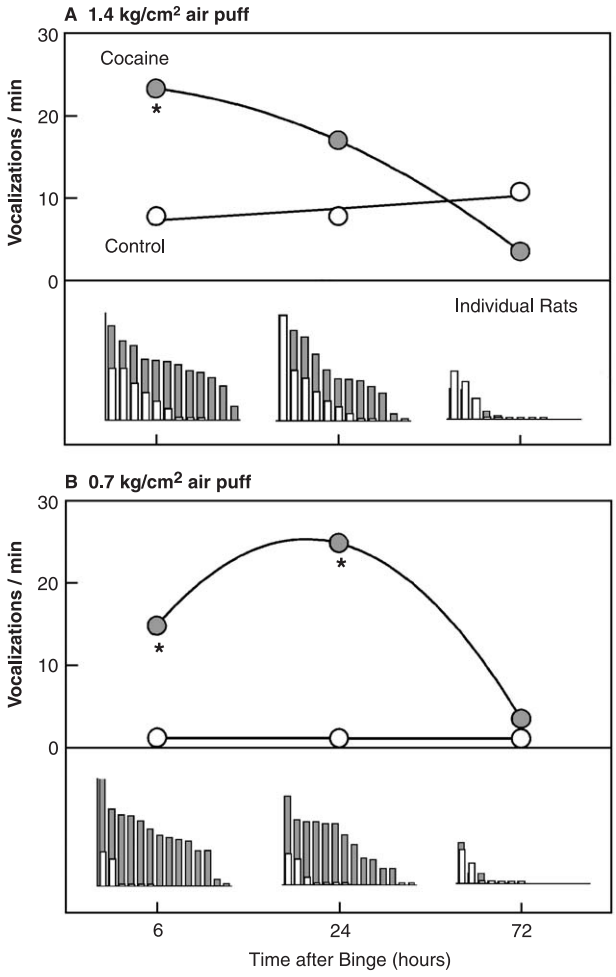

Fig. 1. (A) The group medians for the rate of ultrasonic vocalizations in response to 1.4 kg/cm^2 air puffs, after 48 h of continuous access to cocaine. (B) The group medians for the rate of ultrasonic vocalizations in response to 0.7 kg/cm^2 air puffs, after 48 h of continuous access to cocaine. The *bottom half* of each graph represents data, in descending order of magnitude, from individual rats (*$P<0.05$). [Adapted from Mutschler and Miczek, 1998a.]

Non-contingent infusions of cocaine in yoked control rats also increased the emission of ultrasonic distress calls, but this increment was seen immediately after the cocaine infusions terminated rather than in a delayed fashion. Moreover, the rates of vocalizations were higher at 1, 3 and 5 days of the withdrawal period after cessation of non-contingent cocaine infusions compared to those in rats receiving contingent infusions (see Fig. 2). Increased anxiety-like

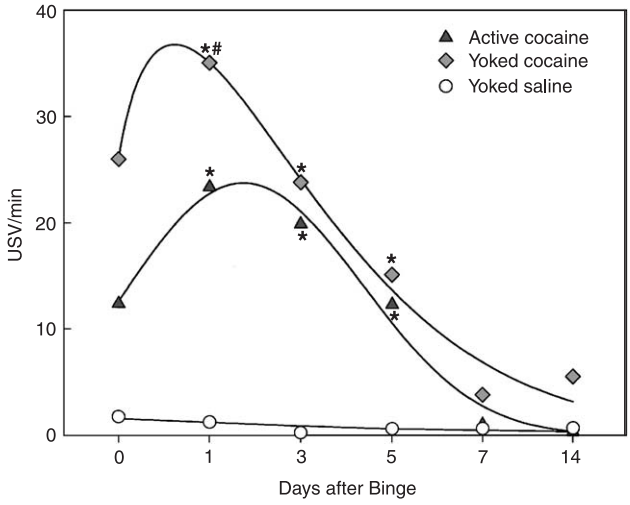

Fig. 2. Rate of ultrasonic vocalizations after 16 h of continuous access to cocaine as a function of the time after the last drug infusion. Group medians are shown for active cocaine self-administering (filled triangles), yoked cocaine (filled diamonds) and yoked saline (open circles) groups. $^{*}P<0.05$ comparing the cocaine groups to the yoked saline group; $^{\#}P<0.05$ comparing the active to the yoked cocaine group. [Adapted from Mutschler et al., 2000.]

responses to passive non-contingent administrations of cocaine are expected since unpredictable and uncontrollable cocaine administrations can serve as an effective stressor (Barry and Buckley, 1966).

The increased rate of emitting ultrasonic vocalizations in response to tactile stimuli during cocaine withdrawal, in both contingently and non-contingently infused rats, returns to baseline levels 7 days after a 16-h binge. Importantly, allowing renewed access to self-administered cocaine 24 h after a single 16-h binge can prevent the heightened emission of ultrasonic distress vocalizations during withdrawal (Mutschler et al., 2001; see Fig. 3). These data support a self-medication hypothesis, in which case the discontinuation of drug taking engenders a distressing affective state that is reversed by renewed access to the very drug from which the individual withdraws (Markou et al., 1998).

An important methodological feature of the study of the anxiety state during stimulant withdrawal is the stimulus used to initiate the response. When a cocaine-withdrawing animal is presented with a mild air puff, it will emit ultrasonic distress calls, whereas a non-withdrawing rat requires a more intense air puff to initiate these responses (Mutschler and Miczek, 1998a; see Fig. 1). These results suggest a dissociation of reflexive responses to stressful stimuli and the emission of anxiety-like vocalizations.

The time course of anxiety-like vocal responses after a 16-h cocaine binge closely model the temporal character of affective disturbances described in various clinical settings (Gawin and Kleber, 1986; Lago and Kosten, 1994). The time course of withdrawal-induced distress ultrasonic vocalizations differ, however, from that of cocaine withdrawal after cessation of limited periods of cocaine access on intracranial self-stimulation thresholds and other models of affective distress. In the latter cases, the withdrawal effects typically diminish within a day or so of terminating cocaine administrations. Daily cocaine availability for 6 h, over 12 days, results in an increase in intracranial self-stimulation reward thresholds that correlate with increased cocaine taking, and both of these effects persist for at least 8 days after cessation of daily extended access (6 h) to cocaine (Ahmed et al., 2002). Intracranial self-stimulation thresholds and cocaine taking behavior were not augmented in animals that had daily access to cocaine for 1 h. These data are interpreted to reflect adaptive neural processes during repeated withdrawal from extended sessions of cocaine taking that contribute to sustained increases in cocaine self-administration. Consistent with this hypothesis, rats emitted anxiety-like ultrasonic vocalizations 24 h after each of three consecutive 16-h cocaine binges, each separated by 10 days of withdrawal, and the withdrawal-induced ultrasonic vocalizations after a third binge could not be reversed by renewed access (Mutschler et al., 2001; see Fig. 4). It is noteworthy that cocaine intake decreased during each of three subsequent 16-h binges, despite cumulative amounts of cocaine intake over the course of each binge that were considerably higher than the cumulative doses during daily 6 h access. The drug-free interval between consecutive access to prolonged cocaine binges appears to be a critical determinant of individually regulated cocaine intake.

The evidence suggests several conclusions about ultrasonic distress vocalizations during stimulant withdrawal. Foremost, the intensity of withdrawal-induced ultrasonic vocalizations depends on the characteristics of experimentally controlled access to cocaine, such as the duration and number of previous access sessions, the route of adminis-

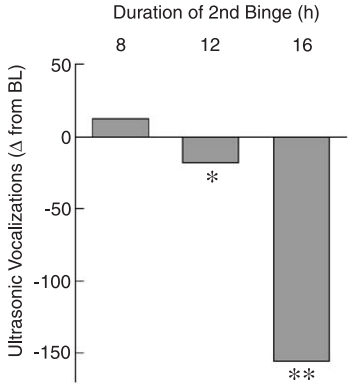

Fig. 3. The number of ultrasonic vocalizations emitted immediately after an 8-, 12- or 16-h cocaine self-administration binge. All data are mean percent change from the number of ultrasonic vocalizations emitted 24 h after an initial 16-h cocaine binge. A negative number of ultrasonic vocalizations indicates that the number of ultrasonic vocalizations emitted during the second binge was lower than during the first binge. $^{*}P<0.05$ and $^{**}P<0.01$, when compared with the mean number of ultrasonic vocalizations emitted following the first 16-h binge. [Adapted from Mutschler et al., 2001.]

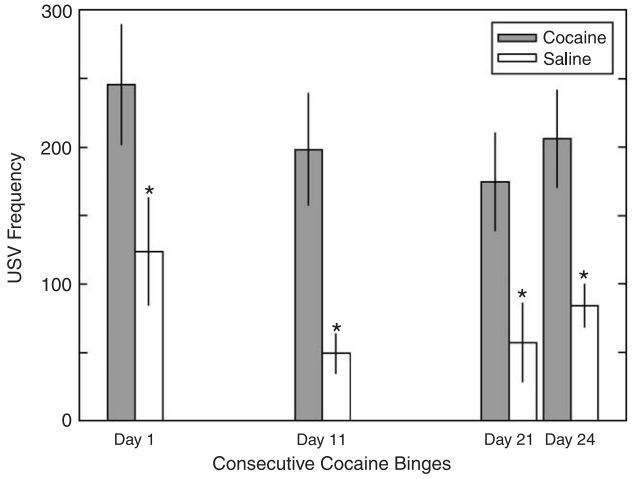

Fig. 4. The mean number of ultrasonic vocalizations emitted in response to tactile stimuli 24 h after binges 1, 2, 3 and immediately following binge 4 in the active cocaine self-administering rats (grey bars) and their yoked saline controls (white bars). $*P<0.05$ compared to controls. [Adapted from Mutschler et al., 2001.]

tration and the dose of cocaine administered. Second, behaviorally contingent control over drug delivery plays a critical role not only in the reinforcing effect of the cocaine infusion, but also the withdrawal, with non-contingent delivered cocaine binges producing immediate anxiety-like ultrasonic vocalizations. This latter observation suggests that experimenter-delivered, behaviorally non-contingent cocaine has aversive effects. Third, the magnitude of a startling stimulus that triggers ultrasonic vocalizations can be adjusted so that relatively mild stimuli become effective in withdrawing animals, but remain ineffective in non-withdrawing animals. This latter effect may reflect a hypersensitivity of cocaine withdrawing subjects to environmental provocations.

4.2. Distress vocalizations during opiate withdrawal

When ultrasonic vocalizations are used as indicators of emotional expressions (“emotional raconteurs”), opiates and opioid peptides have been found to directly modulate affective states expressed when social affiliation is disrupted (Herman and Panksepp, 1978; Panksepp et al., 1978a). Acute administration of morphine, or the μ- or δ-opioid receptor-specific agonists [D-Ala^2,*N*-Me-Phe^4,Gly^5-ol]-enkephalin (DAMGO) or [D-Pen^2,D-Pen^5]-enkephalin (DPDPE), reduce the high rates of ultrasonic vocalizations during separation distress and defensive responses (Haney and Miczek, 1994; Haney and Miczek, 1995; Panksepp et al., 1978b; Vivian and Miczek, 1993b; Vivian and Miczek, 1998, 1999). In addition to the long-duration and low-frequency ultrasonic vocalizations in the 25-kHz range, rats also emit brief pulses of ultrasonic vocalizations in the 55-kHz range and these latter vocalizations are enhanced by acute morphine administrations, interpreted to reflect positive affect (Knutson et al., 1999).

Frequent and intense ultrasonic vocalizations are emitted by rats upon removal of two 75-mg morphine pellets that had been implanted subcutaneously for 3 days (Vivian and Miczek, 1991; see Fig. 5). Specifically, the rate and duration of ultrasounds are increased 6 and 24 h into the withdrawal phase, and this effect begins to decline after 96 h.

The effect of opiate withdrawal on increasing ultrasonic vocalizations parallels the loss in body weight and corresponds to the occurrence of wet dog shakes. Yet, the increase in the production of ultrasonic distress vocalizations can be dissociated from physical signs of dependence (Bläsig et al., 1973; Wei and Way, 1975). In contrast to signs of physical dependence, the production of ultrasonic vocalizations during withdrawal can be influenced by prior social experiences (Vivian and Miczek, 1991; see Fig. 5). A single agonistic confrontation or sexual experience can intensify ultrasonic vocalizations emitted during opiate withdrawal. The emission of ultrasonic vocalizations during opiate withdrawal are similar in frequency and temporal pattern to the ultrasounds in the 22–25-kHz range emitted during post-copulatory activity and defensive-submissive responses, further suggesting that the emission of ultrasounds during withdrawal may be an expression of affective distress.

Morphine withdrawal early in life can be identified by behavioral observations (Jones and Barr, 1995), as well as

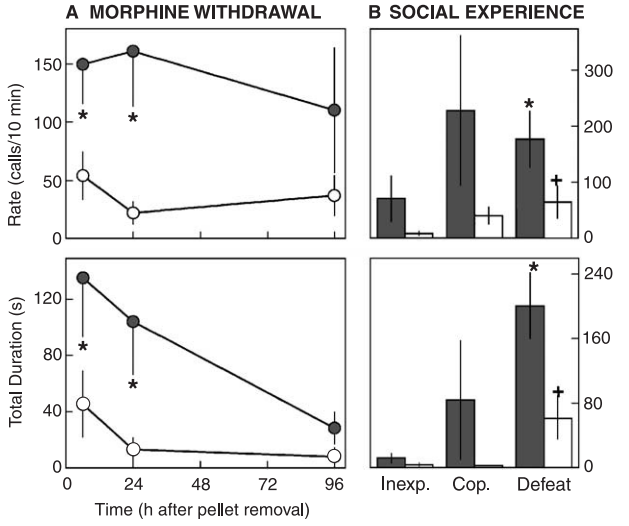

Fig. 5. (A) Mean rate (calls/10 min, *top*) and total duration (s, *bottom*) of ultrasonic vocalizations throughout 96 h withdrawal for morphine (filled circles) and placebo (open circles) implanted rats. Error bars denote ± 1 S.E.M.; $*P<0.05$ compared to placebo controls. Each point is the combined vocalizations of socially inexperienced, copulatory experienced and defeat experienced rats. (B) Mean rate (calls/10 min, *top*) and total duration (s, *bottom*) of ultrasonic vocalizations for socially inexperienced (Inexp.), copulatory experienced (Cop.) and defeat experienced (Defeat) rats. Each bar is the combined vocalizations at 6, 24 and 96 h after removal of morphine (filled bars) or placebo (open bars) pellet removal. Error bars denote ± 1 S.E.M.; $*P<0.05$ from socially inexperienced morphine group and $^{+}P<0.05$ compared to inexperienced placebo group. [Adapted from Vivian and Miczek, 1991.]

by ultrasonic and audible vocalizations (Barr and Wang, 1992; Jones et al., 2002). Seven-day-old infant rats that receive morphine 10.0 mg/kg, twice a day, for the first 7 days after birth, emit more ultrasonic vocalizations during naloxone-precipitated withdrawal (Barr and Wang, 1992). Even a single morphine injection (10.0 mg/kg) on post-natal day 7 can produce acute morphine withdrawal that is identified by the production of audible vocalizations when withdrawal is precipitated by naltrexone (Jones et al., 2002). Vocalizations during opiate withdrawal in rat pups may represent an expression of dysphoria, as suggested by the similarity of these calls to those emitted by pups while coping with highly aversive environmental conditions (Bell et al., 1971; Hofer and Shair, 1987).

Similar to opiates, discontinuation of chronic alcohol consumption engenders the onset of a severe behavioral, physiological and psychological withdrawal symptom (Heinz et al., 1998; Mello, 1973). Preclinical studies have demonstrated the severity of dependence to alcohol by measuring behavioral and physiological changes that are interpreted to reflect the anxiogenic effects of alcohol withdrawal (File et al., 1993; Lal et al., 1991; Moy et al., 1997). When alcohol-withdrawing rats are startled, they too emit increased rates of ultrasonic vocalizations (Moy et al., 2000). Likewise, the cessation of administering clinically relevant doses of diazepam to rats gives rise to the production of distress ultrasonic vocalizations within the first 24 h of withdrawal (Miczek and Vivian, 1993; Vivian et al., 1994a). Similarly, humans report a heightened state of emotional distress during withdrawal from prescribed benzodiazepine medication (Rickels et al., 1990). Despite these clinical observations (Lader, 1994), only a limited number of preclinical models have readily detected the occurrence of behavioral deficits during withdrawal from benzodiazepine administration (File and Andrews, 1991; Lukas and Griffiths, 1982; Votava et al., 2001). In contrast to acute opiate dependence, withdrawal effects after a single administration of clinically relevant doses of benzodiazepines are difficult to produce in animals (Martin et al., 1982). The emission of ultrasonic vocalizations during benzodiazepine and alcohol withdrawal may be a potential indicator of anxiety-like distress that is useful for quantifying aspects of neural adaptations to benzodiazepine and alcohol indicative of dependence.

In addition to the well-known withdrawal sign "scream-on-touch" that is audible to the human experimenter who examines opiate withdrawal in rats (Higgins et al., 1991; Wei et al., 1973a), the ultrasonic distress calls are prominent features in rats that undergo withdrawal from opiates. Their delayed emergence and prolonged emission may reflect the time course of affective distress, both in infant and adult animals. It would be instructive to learn whether or not withdrawal from self-administered vs. experimenter-delivered opiates results in differential magnitude and time course of affective distress as indicated by the production of ultrasonic vocalizations.

5. Future perspectives

High-pitched vocalizations, particularly certain types of ultrasonic vocalizations in rodents, represent responses that communicate affective and anxiety-like expressions. In addition to their communicative role in maternal separation distress, sexual satiety, defensive, submissive and nociceptive responses, certain types of rodent ultrasonic vocalizations are also prominent features of withdrawal from diverse classes of substances such as opiates, alcohol, benzodiazepines and psychomotor stimulants. These latter vocalizations are emitted even in the absence of an audience and are readily triggered by mild startling stimuli. The peak rate and time course of these vocalizations are directly related to the magnitude and duration of the preceding drug exposure as well as to whether or not the drug was self-administered or delivered by the experimenter. The neural circuit for ultrasonic vocalizations comprises limbic modulation of mesencephalic pathways that innervate the vocal apparatus (see Fig. 6). Alarm calls during distress states are mediated by a medial cholinoceptive pathway, originating in the laterodorsal tegmental nucleus (Brudzynski, 2001; Satoh and Fibiger, 1986). This medial pathway contains cholinergic efferents that project to hypothalamic nuclei and the preoptic area, in addition to accumbal, septal and forebrain regions (Cornwall et al., 1990; Consolo et al., 1990; Brudzynski and Bihari, 1990).

Sites in the periaqueductal grey modulate anxiety-like vocalizations (Bandler and Carrive, 1988; Jürgens and Pratt, 1979). The periaqueductal grey receives direct and indirect

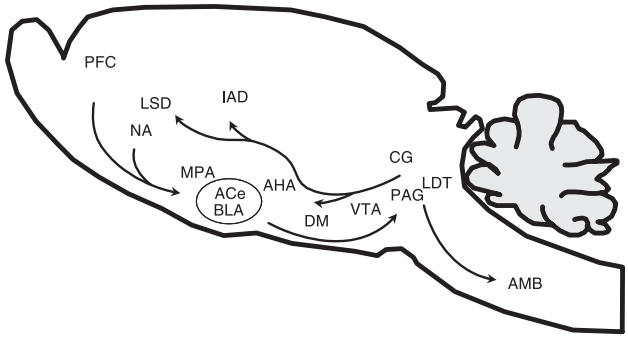

Fig. 6. Parasagittal illustration of brain areas that are significant for the production of anxiety-like distress vocalizations and that are susceptible to adaptative responses during drug withdrawal states. Represented are primarily those areas within the medial cholinoceptive vocalization strip (Brudzynski, 2001) that are located approximately 0.9 mm lateral from the midsagittal plane (Paxinos and Watson, 1986). Also included are the central and basolateral amygdaloid nuclei that are located about 4.2 mm lateral and the ambiguus nucleus located 1.9 mm lateral to the midline. Abbreviations: ACe: central amygdaloid nucleus, AHA: anterior hypothalamic area, AMB: ambiguus nucleus, BLA: basolateral amygdaloid nucleus, CG: central gray, DM: dorsomedial hypothalamic nucleus, IAD: interanterodorsal thalamic nucleus, LDT: laterodorsal tegmental nucleus, LSD: dorsal portion of the lateral septal nucleus, MPA: medial preoptic area, NA: nucleus accumbens, PAG: periaqueductal grey, PFC: prefrontal cortex, VTA: ventral tegmental area.

modulation from the amygdala and it sends projections to specific areas of the brainstem, including the nucleus ambiguus (Da Costa Gomez and Behbehani, 1995; Holstege et al., 1997). The nucleus ambiguus innervates the vocal apparatus (Yajima et al., 1982; Holstege, 1989). Cells in the periaqueductal grey are significantly activated during withdrawal from opiates and stimulants, and these neural adaptations correspond to the peak onset of anxiety-like responses, including the production of distress-vocalizations (Frenois et al., 2002; Mutschler et al., 2000). It will be informative to learn more about how the vocalization circuit interacts with the ones subserving self-administration of alcohol, opiates and psychomotor stimulants.

References

Ahmed, S.H., Kenny, P.J., Koob, G.F., Markou, A., 2002. Neurobiological evidence for hedonic allostasis associated with escalating cocaine use. Nat. Neurosci. 5, 625–626.

Allan, A.M., Harris, R.A., 1986. Gamma-aminobutyric acid agonists and antagonists alter chloride flux across brain membranes. Mol. Pharmacol. 29, 497–505.

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. American Psychiatric Association, Washington, DC.

Bandler, R., Carrive, P., 1988. Integrated defense reaction elicited by excitatory amino acid microinjection in the midbrain periaqueductal region of the unrestrained cat. Brain Res. 439, 95–106.

Barfield, R.J., Geyer, L.A., 1972. Sexual behavior: ultrasonic post-ejaculatory song of the male rat. Science 176, 1349–1350.

Barfield, R.J., Geyer, L.A., 1975. The ultrasonic postejaculatory vocalization and the postejaculatory refractory period of the male rat. J. Comp. Physiol. Psychol. 88, 723–734.

Barfield, R.J., Auerbach, P., Geyer, L.A., McIntosh, T.K., 1979. Ultrasonic vocalizations in rat sexual behavior. Am. Zool. 19, 469–480.

Barlow, D.H., Wincze, J., 1998. DSM-IV and beyond: what is generalized anxiety disorder? Acta Psychiatr. Scand. 98, 23–29.

Barr, A.M., Phillips, A.G., 1999. Withdrawal following repeated exposure to *d*-amphetamine decreases responding for a sucrose solution as measured by a progressive ratio schedule of reinforcement. Psychopharmacology 141, 99–106.

Barr, G.A., Wang, S.N., 1992. Tolerance and withdrawal to chronic morphine treatment in the week-old rat pup. Eur. J. Pharmacol. 215, 35–42.

Barr, A.M., Fiorino, D.F., Phillips, A.G., 1999. Effects of withdrawal from an escalating dose schedule of *d*-amphetamine on sexual behavior in the male rat. Pharmacol. Biochem. Behav. 64, 597–604.

Barros, H., Miczek, K.A., 1996. Withdrawal from oral cocaine in rats: ultrasonic vocalizations and tactile startle. Psychopharmacology 125, 379–384.

Barry III, H., Buckley, J.P., 1966. Drug effects on animal performance and the stress syndrome. J. Pharm. Sci. 55, 1159–1183.

Basso, A.M., Spina, M., Rivier, J., Vale, W., Koob, G.F., 1999. Corticotropin-releasing factor antagonist attenuates the "anxiogenic-like" effect in the defensive burying paradigm but not in the elevated plus-maze following chronic cocaine in rats. Psychopharmacology 145, 21–30.

Bell, R.W., Nitshke, W., Gorry, T.H., Zachman, T.A., 1971. Infantile stimulation and ultrasonic signaling: a possible mediator of early handling phenomena. Dev. Psychobiol. 4, 181–191.

Bentley, G.E., Wingfield, J.C., Morton, M.L., Ball, G.F., 2000. Stimulatory effects on the reproductive axis in female songbirds by conspecific and heterospecific male song. Horm. Behav. 37, 179–189.

Bläsig, J., Herz, A., Reinhold, K., Zieglgansberger, S., 1973. Development of physical dependence on morphine in respect to time and dosage and quantification of the precipitated withdrawal syndrome in rats. Psychopharmacologia 33, 19–38.

Brady, J.V., 1956. Assessment of drug effects on emotional behavior. Science 123, 1033–1034.

Brady, L.S., Holtzman, S.G., 1980. Schedule-controlled behavior in the morphine-dependent and post-dependent rat. Psychopharmacology 70, 11–18.

Brudzynski, S.M., 2001. Pharmacological and behavioral characteristics of 22 kHz alarm calls in rats. Neurosci. Biobehav. Rev. 25, 611–617.

Brudzynski, S.M., Bihari, F., 1990. Ultrasonic vocalization in rats produced by cholinergic stimulation of the brain. Neurosci. Lett. 109, 222–226.

Brudzynski, S.M., Eckersdorf, B., 1988. Vocalization accompanying emotional-aversive response induced by carbachol in the cat: reproducibility and dose-response study. Neuropsychopharmacology 1, 311–320.

Burgdorf, J., Knutson, B., Panksepp, J., Ikemoto, S., 2001. Nucleus accumbens amphetamine microinjections unconditionally elicit 50-kHz ultrasonic vocalizations in rats. Behav. Neurosci. 115, 940–944.

Campbell, J.C., Seiden, L.S., 1973. Performance influence on the development of tolerance to amphetamine. Pharmacol. Biochem. Behav. 1, 703–708.

Caul, W.F., Jones, J.R., Barrett, R.J., 1988. Amphetamine's effects on food consumption and body weight: the role of adaptive processes. Behav. Neurosci. 102, 441–450.

Consolo, S., Bertorelli, R., Forloni, G.L., Butchler, L.L., 1990. Cholinergic neurons of the pontomesencephalic tegmentum release acetylcholine in the basal nuclear complex of freely moving rats. Neuroscience 37, 717–723.

Cornwall, J., Cooper, J.D., Phillipson, O.T., 1990. Afferent and efferent connections of the laterodorsal tegmental nucleus in the rat. Brain Res. Bull. 25, 271–284.

Costall, B., Jones, B.J., Kelly, M.E., Naylor, R.J., Onaivi, E.S., Tyers, M.B., 1990. Ondansetron inhibits a behavioural consequence of withdrawing from drugs of abuse. Pharmacol. Biochem. Behav. 36, 339–344.

Covington III, H.E., Miczek, K.A., 2001. Repeated social-defeat stress, cocaine or morphine: effects on behavioral sensitization and intravenous cocaine self-administration "binges". Psychopharmacology 158, 388–398.

Da Costa Gomez, T.M., Behbehani, M.M., 1995. An electrophysiological charecterization of the projection from the central nucleus of the amygdala to the periaqueductal gray of the rat: the role of opioid receptors. Brain Res. 689, 21–31.

Davis, M., Gallager, D.W., 1988. Continuous slow release of low levels of diazepam produces tolerance to its depressant and anxiolytic effects on the startle reflex. Eur. J. Pharmacol. 150, 23–33.

DeRossett, S.E., Holtzman, S.G., 1985. Effects of opiate antagonists and putative K agonists on unpunished and punished operant behavior in the rat. Psychopharmacology 86, 386–391.

DeVry, J., Benz, U., Schreiber, R., Traber, J., 1993. Shock-induced ultrasonic vocalization in young adult rats: a model for testing putative anti-anxiety drugs. Eur. J. Pharmacol. 249, 331–339.

Ettenberg, A., Raven, M.A., Danluck, D.A., Necessary, B.D., 1999. Evidence for opponent-process actions of intravenous cocaine. Pharmacol. Biochem. Behav. 64, 507–512.

Farrell, M., 1994. Opiate withdrawal. Addiction 89, 1471–1475.

File, S.E., Andrews, N., 1991. Low but not high doses of buspirone reduce the anxiogenic effects of diazepam withdrawal. Psychopharmacology 105, 578–582.

File, S.E., Lister, R.G., Nutt, D.J., 1982. The anxiogenic action of benzodiazepine antagonists. Neuropharmacology 21, 1033–1037.

File, S.E., Andrews, N., Al Farhan, M., 1993. Anxiogenic responses of rats on withdrawal from chronic ethanol treatment: effects of tianeptine. Alcohol Alcohol. 28, 281–286.

Fish, E.W., Sekinda, M., Ferrari, P.F., Dirks, A., Miczek, K.A., 2000. Distress vocalizations in maternally separated mouse pups: modulation via 5-HT_{1A}, 5-HT_{1B} and $GABA_A$ receptors. Psychopharmacology 149, 277–285.

Ford, R.D., Balster, R.L., 1976. Schedule-controlled behavior in the morphine-dependent rat. Pharmacol. Biochem. Behav. 4, 569–573.
Frenois, F., Cador, M., Caille, S., Stinus, L., Le Moine, C., 2002. Neural correlates of the motivational and somatic components of naloxone-precipitated morphine withdrawal. Eur. J. Neurosci. 16, 1377–1389.
Gardner, C.R., 1985. Distress vocalization in rat pups: a simple screening method for anxiolytic drugs. J. Pharmacol. Methods 14, 181–187.
Gawin, F.H., 1989. Cocaine abuse and addiction. J. Fam. Pract. 29, 193–197.
Gawin, F.H., 1991. Cocaine addiction: psychology and neurophysiology. Science 251, 1580–1586.
Gawin, F.H., Ellinwood Jr., E.H., 1988. Cocaine and other stimulants: actions, abuse, and treatment. N. Engl. J. Med. 318, 1173–1182.
Gawin, F.H., Kleber, H.D., 1986. Abstinence symptomatology and psychiatric diagnosis in cocaine abusers: clinical observations. Arch. Gen. Psychiatry 43, 107–113.
Geller, I., Seifter, J., 1960. The effects of meprobamate, barbiturates, *d*-amphetamine and promazine on experimentally induced conflict in the rat. Psychopharmacologia 1, 482–492.
Glick, S.D., Cox, R.D., 1977. Changes in sensitivity to operant effects of dopaminergic and cholinergic agents following morphine withdrawal in rats. Eur. J. Pharmacol. 42, 303–306.
Goldberg, S.R., Schuster, C.R., 1967. Conditioned suppression by a stimulus associated with nalorphine in morphine-dependent monkeys. J. Exp. Anal. Behav. 10, 235–242.
Goldstein, A., 1972. Heroin addiction and the role of methadone in its treatment. Arch. Gen. Psychiatry 26, 291–297.
Goldstein, A., 1994. Addiction: From Biology to Drug Policy. W.H. Freeman, New York.
Hainsworth, F.R., 1967. Saliva spreading, activity, and body temperature regulation in the rat. Am. J. Physiol. 212, 1288–1292.
Haney, M., Miczek, K.A., 1994. Ultrasounds emitted by female rats during agonistic interactions: effects of morphine and naltrexone. Psychopharmacology 114, 441–448.
Haney, M., Miczek, K.A., 1995. Delta opioid receptors: reflexive, defensive and vocal affective responses in female rats. Psychopharmacology 121, 204–212.
Heinz, A., Ragan, P., Jones, D.W., Hommer, D., Williams, W., Knable, M.B., Gorey, J.G., Doty, L., Geyer, C., Lee, K.S., Coppola, R., Weinberger, D.R., Linnoila, M., 1998. Reduced central serotonin transporters in alcoholism. Am. J. Psychiatry 155, 1544–1549.
Heishman, S.J., Stitzer, M.L., Bigelow, G.E., Liebson, I.A., 1989. Acute opioid physical dependence in postaddict humans: naloxone dose effects after brief morphine exposure. J. Pharmacol. Exp. Ther. 248, 127–134.
Henry, D.J., Hu, X.T., White, F.J., 1998. Adaptations in the mesoaccumbens dopamine system resulting from repeated administration of dopamine D_1 and D_2 receptor-selective agonists: relevance to cocaine sensitization. Psychopharmacology 140, 233–242.
Herman, B., Panksepp, J., 1978. Effect of morphine and naloxone on separation distress and approach attachment: evidence for opiate mediation of social affect. Pharmacol. Biochem. Behav. 9, 213–220.
Higgins, G.A., Nguyen, P., Joharchi, N., Sellers, E.M., 1991. Effects of 5-HT_3 receptor antagonists on behavioural measures of naloxone-precipitated opioid withdrawal. Psychopharmacology 105, 322–328.
Hill, R.T., 1970. Facilitation of conditioned reinforcement as a mechanism of psychomotor stimulation. In: Costa, E., Garattini, S. (Eds.), International Symposium on Amphetamines and Related Compounds. Raven Press, New York, pp. 781–795.
Hofer, M.A., 1996. Multiple regulators of ultrasonic vocalization in the infant rat. Psychoneuroendocrinology 21, 203–217.
Hofer, M.A., Shair, H.N., 1987. Isolation distress in 2-week old rats: influence of home cage, social companions, and prior experience with littermates. Dev. Psychobiol. 20, 465–476.
Holstege, G., 1989. Anatomical study of the final common pathway for vocalization in the cat. J. Comp. Neurol. 284, 242–252.
Holstege, G., Kerstens, L., Moes, M.C., Vanderhorst, V.G.J.M., 1997. Evidence for a periaqueductal gray–nucleus retroambiguus–spinal cord pathway in the rat. Neuroscience 80, 587–598.
Jaffe, J.H., 1985. Drug addiction and drug abuse. In: Gilman, A. (Ed.), Goodman and Gilman's The Pharmacological Basis of Therapeutics. Macmillan, New York, pp. 532–581.
Jaffe, J.H., 1992. Current concepts of addiction. In: O'Brian, C.P. (Ed.), Addictive States. Raven Press, New York, pp. 1–21.
Jensen, M.A., Thompson, T.I., 1982. Interaction of methadone and pentobarbital on chained fixed-interval performance in pigeons. Pharmacol. Biochem. Behav. 16, 271–278.
Jones, K.L., Barr, G.A., 1995. Ontogeny of morphine withdrawal in the rat. Behav. Neurosci. 109, 1189–1198.
Jones, K.L., Zhu, H.B., Jenab, S., Du, T., Inturrisi, C.E., Barr, G.A., 2002. Attenuation of acute morphine withdrawal in the neonatal rat by the competitive NMDA receptor antagonist LY235959. Neuropsychopharmacology 26, 301–310.
Jung, M.E., Lal, H., Gatch, M.B., 2002. The discriminative stimulus effects of pentylenetetrazol as a model of anxiety: recent developments. Neurosci. Biobehav. Rev. 26, 429–439.
Jürgens, U., 1983. Control of vocal aggression in squirrel monkeys. In: Capranica, R.R. (Ed.), Advances in Vertebrate Neuroethology. Plenum, New York, pp. 1087–1102.
Jürgens, U., Pratt, R., 1979. Role of periaqueductal grey in vocal expression of emotion. Brain Res. 167, 367–378.
Kantak, K.M., Miczek, K.A., 1988. Social, motor, and autonomic signs of morphine withdrawal: differential sensitivities to catecholaminergic drugs in mice. Psychopharmacology 96, 468–476.
Kleven, M.S., Woolverton, W.L., 1991. Effects of continuous cocaine administration on schedule-controlled behavior in rhesus monkeys. Behav. Pharmacol. 2, 471–480.
Knutson, B., Burgdorf, J., Panksepp, J., 1999. High-frequency ultrasonic vocalizations index conditioned pharmacological reward in rats. Physiol. Behav. 66, 639–643.
Kokkinidis, L., Zacharko, R.M., 1980. Response sensitization and depression following long-term amphetamine treatment in a self-stimulation paradigm. Psychopharmacology 68, 73–76.
Kokkinidis, L., Zacharko, R.M., Predy, P.A., 1980. Post-amphetamine depression of self-stimulation responding from the substantia nigra: reversal by tricyclic antidepressants. Pharmacol. Biochem. Behav. 13, 379–383.
Koob, G.F., Le Moal, M., 2001. Drug addiction, dysregulation of reward, and allostasis. Neuropsychopharmacology 24, 97–129.
Koob, G.F., Caine, S.B., Parsons, L., Markou, A., Weiss, F., 1997. Opponent process model and psychostimulant addiction. Pharmacol. Biochem. Behav. 57, 513–521.
Kosten, T.R., Gawin, F.H., Rounsaville, B.J., Kleber, H.D., 1986. Cocaine abuse among opioid addicts: demographic and diagnostic factors in treatment. Am. J. Drug Alcohol Abuse 12, 1–16.
Kuczenski, R., Segal, D.S., Aizenstein, M.L., 1991. Amphetamine, cocaine, and fencamfamine: relationship between locomotor and stereotypy response profiles and caudate and accumbens dopamine dynamics. J. Neurosci. 11, 2703–2712.
Lader, M., 1994. Benzodiazepines: a risk-benefit profile. CNS Drugs 1, 377–387.
Lago, J.A., Kosten, T.R., 1994. Stimulant withdrawal. Addiction 89, 1477–1481.
Lal, H., Prather, P.L., Rezazadeh, S.M., 1991. Anxiogenic behavior in rats during acute and protracted ethanol withdrawal: reversal by buspirone. Alcohol 8, 467–471.
Leith, N.J., Barrett, R.J., 1976. Amphetamine and the reward system: evidence for tolerance and post-drug depression. Psychopharmacologia 46, 19–25.
Leith, N.J., Barrett, R.J., 1980. Effects of chronic amphetamine or reserpine on self-stimulation responding: animal model of depression? Psychopharmacology 72, 9–15.
Lilly, S.M., Tietz, E.I., 2000. Chronic cocaine differentially affects diaze-

pam's anxiolytic and anticonvulsant actions: relationship to $GABA_A$ receptor subunit expression. Brain Res. 882, 139–148.
Lister, R.G., 1987. The use of a plus-maze to measure anxiety in the mouse. Psychopharmacology 92, 180–185.
Lorenzetti, O.J., Sancilio, L.F., 1970. Morphine dependent rats as a model for evaluating potential addiction liability of analgesic compounds. Arch. Int. Pharmacodyn. Ther. 183, 391–402.
Lukas, S.E., Griffiths, R.R., 1982. Precipitated withdrawal by a benzodiazepine receptor antagonist (Ro 15-1788) after 7 days of diazepam. Science 217, 1161–1163.
Markou, A., Koob, G.F., 1991. Postcocaine anhedonia—an animal model of cocaine withdrawal. Neuropsychopharmacology 4, 17–26.
Markou, A., Koob, G.F., 1992. Bromocriptine reverses the elevation in intracranial self-stimulation thresholds observed in rat model of cocaine withdrawal. Neuropsychopharmacology 7, 213–224.
Markou, A., Hauger, R.L., Koob, G., 1992. Desmethylimipramine attenuates cocaine withdrawal in rats. Psychopharmacology 109, 305–314.
Markou, A., Kosten, T.R., Koob, G.F., 1998. Neurobiological similarities in depression and drug dependence: a self-medication hypothesis. Neuropsychopharmacology 18, 135–174.
Marshall, I., Weinstock, M., 1971. Quantitative method for assessing one symptom of the withdrawal syndrome in mice after chronic morphine administration. Nature 234, 223–224.
Martin, W.R., Wikler, A., Eades, C.G., Pescor, F.T., 1963. Tolerance to and physical dependence on morphine in rats. Psychopharmacologia 4, 247–260.
Martin, W.R., McNicholas, L.F., Cherian, S., 1982. Diazepam and pentobarbital dependence in the rat. Life Sci. 31, 721–730.
McMillan, D.E., 1973. Effects of narcotics and narcotic antagonists on operant behavior. Adv. Biochem. Psychopharmacol. 8, 345–359.
Mello, N.K., 1973. Theoretical review: a review of methods to induce alcohol addiction in animals. Pharmacol. Biochem. Behav. 1, 89–101.
Meyer, D.R., Sparber, S.B., 1977. Evidence of possible opiate dependence during the behavioral depressant action of a single dose of morphine. Life Sci. 21, 1087–1093.
Miczek, K.A., Vivian, J.A., 1993. Automatic quantification of withdrawal from 5-day diazepam in rats: ultrasonic distress vocalizations and hyperreflexia to acoustic startle stimuli. Psychopharmacology 110, 379–382.
Miczek, K.A., Winslow, J.T., 1987. Analgesia and decrement in operant performance in socially defeated mice: selective cross-tolerance to morphine and antagonism by naltrexone. Psychopharmacology 92, 444–451.
Miczek, K.A., Tornatzky, W., Vivian, J.A., 1991. Ethology and neuropharmacology: rodent ultrasounds. In: Olivier, B. (Ed.), Animal Models in Psychopharmacology. Birkhauser, Basel, pp. 409–427.
Miczek, K.A., Weerts, E.M., Vivian, J.A., Barros, H.M., 1995. Aggression, anxiety and vocalizations in animals: $GABA_A$ and 5-HT anxiolytics. Psychopharmacology 121, 38–56.
Moy, S.S., Knapp, D.J., Criswell, H.E., Breese, G.R., 1997. Flumazenil blockade of anxiety following ethanol withdrawal in rats. Psychopharmacology 131, 354–360.
Moy, S.S., Knapp, D.J., Duncan, G.E., Breese, G.R., 2000. Enhanced ultrasonic vocalization and fos protein expression following ethanol withdrawal: effects of flumazenil. Psychopharmacology 152, 208–215.
Mutschler, N.H., Miczek, K.A., 1998a. Withdrawal from IV cocaine "binges" in rats: ultrasonic distress calls and startle. Psychopharmacology 135, 161–168.
Mutschler, N.H., Miczek, K.A., 1998b. Withdrawal from a self-administered or non-contingent cocaine binge: differences in ultrasonic distress vocalizations in rats. Psychopharmacology 136, 402–408.
Mutschler, N.H., Miczek, K.A., Hammer Jr., R.P., 2000. Reduction of *zif268* messenger RNA expression during prolonged withdrawal following "binge" cocaine self-administration in rats. Neuroscience 100, 531–538.
Mutschler, N.H., Covington III, H.E., Miczek, K.A., 2001. Repeated self-administered cocaine "binges" in rats: effects on cocaine intake and withdrawal. Psychopharmacology 154, 292–300.
Negus, S.S., Burke, T.F., Medzihradsky, F., Woods, J.H., 1993. Effects of opioid agonists selective for mu, kappa and delta opioid receptors on schedule-controlled responding in rhesus monkeys: antagonism by quadazocine. J. Pharmacol. Exp. Ther. 267, 896–903.
Nyby, J., Whitney, G., 1978. Ultrasonic communication of adult myomorph rodents. Neurosci. Biobehav. Rev. 2, 1–14.
Olivier, B., Molewijk, H.E., Van der Heyden, J.A.M., Van Oorschot, R., Ronken, E., Mos, J., Miczek, K.A., 1998. Ultrasonic vocalizations in rat pups: effects of serotonergic ligands. Neurosci. Biobehav. Rev. 23, 215–227.
Paine, T.A., Jackman, S.L., Olmstead, M.C., 2002. Cocaine-induced anxiety: alleviation by diazepam, but not buspirone, dimenhydrinate or diphenhydramine. Behav. Pharmacol. 13, 511–523.
Panksepp, J., Herman, B., Conner, R., Bishop, P., Scott, J.P., 1978a. The biology of social attachments: opiates alleviate separation distress. Biol. Psychiatry 13, 607–618.
Panksepp, J., Vilberg, T., Bean, N.J., Coy, D.H., Kastin, A.J., 1978b. Reduction of distress vocalization in chicks by opiate-like peptides. Brain Res. Bull. 3, 663–667.
Paxinos, G., Watson, C., 1986. The Rat Brain in Stereotaxic Coordinates. Academic Press, Sydney.
Pellow, S., Chopin, P., File, S.E., Briley, M., 1985. Validation of open: closed arm entries in an elevated plus-maze as a measure of anxiety in the rat. J. Neurosci. Methods 14, 149–167.
Pliakas, A.M., Carlson, R.R., Neve, R.L., Konradi, C., Nestler, E.J., Carlezon, W.A., 2001. Altered responsiveness to cocaine and increased immobility in the forced swim test associated with elevated cAMP response element-binding protein expression in nucleus accumbens. J. Neurosci. 21, 7397–7403.
Ploog, D., 1988. Neurobiology and pathology of subhuman vocal communication and human speech. In: Todt, D. (Ed.), Primate Vocal Communication. Springer-Verlag, Berlin, pp. 195–212.
Redmond, D.E., Krystal, J.H., 1984. Multiple mechanisms of withdrawal from opioid drugs. Annu. Rev. Neurosci. 7, 443–478.
Rickels, K., Schweizer, E., Case, W.G., Greenblatt, D.J., 1990. Long-term therapeutic use of benzodiazepines: I. Effects of abrupt discontinuation. Arch. Gen. Psychiatry 47, 899–907.
Rodgers, R.J., 1997. Animal models of 'anxiety': where next? Behav. Pharmacol. 8, 477–496.
Rowlett, J.K., Tornatzky, W., Cook, J.M., Ma, C.R., Miczek, K.A., 2001. Zolpidem, triazolam, and diazepam decrease distress vocalizations in mouse pups: differential antagonism by flumazenil and beta-carboline-3-carboxylate-t-butyl ester (β-CCt). J. Pharmacol. Exp. Ther. 297, 247–253.
Sales, G.D., Pye, J.D., 1974. Ultrasonic Communication by Animals. Chapman and Hall, London.
Sarnyai, Z., Biro, E., Gardi, J., Vecsernyes, M., Julesz, J., Telegdy, G., 1995. Brain corticotropin-releasing factor mediates 'anxiety-like' behavior induced by cocaine withdrawal in rats. Brain Res. 675, 89–97.
Satel, S.L., Price, L.H., Palumbo, J.M., McDougle, C.J., Krystal, J.H., Gawin, F., Charney, D.S., Heninger, G.R., Kleber, H.D., 1991. Clinical phenomenology and neurobiology of cocaine abstinence: a prospective inpatient study. Am. J. Psychiatry 148, 1712–1716.
Satoh, K., Fibiger, H.C., 1986. Cholinergic neurons of the laterodorsal tegmental nucleus, efferent and afferent connections. J. Comp. Neurol. 253, 277–302.
Scherer, K.R., Zei, B., 1988. Vocal indicators of affective disorders. Psychother. Psychosom. 49, 179–186.
Schulteis, G., Markou, A., Gold, L.H., Stinus, L., Koob, G.F., 1994. Relative sensitivity to naloxone of multiple indices of opiate withdrawal: a quantitative dose-response analysis. J. Pharmacol. Exp. Ther. 271, 1391–1398.
Schulteis, G., Heyser, C.J., Koob, G.F., 1997. Opiate withdrawal signs precipitated by naloxone following a single exposure to morphine: potentiation with a second morphine exposure. Psychopharmacology 129, 56–65.
Schwartz, A.S., Woolf, B., Hedin, C., Marchok, P., 1978. Dissociation of

discrimination of skin warming from skin cooling by morphine in monkeys. Brain Res. 156, 206–210.
Solomon, R.L., 1980. The opponent-process theory of acquired motivation: the costs of pleasure and the benefits of pain. Am. Psychol. 35, 691–712.
Stutzmann, G.E., McEwen, B.S., LeDoux, J.E., 1998. Serotonin modulation of sensory inputs to the lateral amygdala: dependency on corticosterone. J. Neurosci. 18, 9529–9538.
Tembrock, G., 1975. Biological basis of behavior regulation. Z. Gesamte Inn. Med. 30 (Suppl. 15).
Terwilliger, R.Z., Beitner-Johnson, D., Sevarino, K.A., Crain, S.M., Nestler, E.J., 1991. A general role for adaptations in G-proteins and the cyclic AMP system in mediating the chronic actions of morphine and cocaine on neuronal function. Brain Res. 548, 100–110.
Thomas, D.A., Takahashi, L.K., Barfield, R.J., 1983. Analysis of ultrasonic vocalizations emitted by intruders during aggressive encounters among rats (*Rattus norvegicus*). J. Comp. Psychol. 97, 201–206.
Thompson, T., Trombley, J., Luke, D., Lott, D., 1970. Effects of morphine on behavior maintained by four simple food-reinforcement schedules. Psychopharmacologia 17, 182–192.
Tornatzky, W., Miczek, K.A., 2000. Cocaine self-administration ''binges'': transition from behavioral and autonomic regulation toward homeostatic dysregulation in rats. Psychopharmacology 148, 289–298.
van der Poel, A.M., Miczek, K.A., 1991. Long ultrasonic calls in male rats following mating, defeat and aversive stimulation: frequency modulation and bout structure. Behaviour 119, 127–142.
Vellucci, S.V., Martin, P.J., Everitt, B.J., 1988. The discriminative stimulus produced by pentylenetetrazol: effects of systemic anxiolytics and anxiogenics, aggressive defeat and midazolam or muscimol infused into the amygdala. J. Psychopharmacol. 2, 80–93.
Vivian, J.A., Miczek, K.A., 1991. Ultrasounds during morphine withdrawal in rats. Psychopharmacology 104, 187–193.
Vivian, J.A., Miczek, K.A., 1993a. Diazepam and gepirone selectively attenuate either 20–32 or 32–64 kHz ultrasonic vocalizations during aggressive encounters. Psychopharmacology 112, 66–73.
Vivian, J.A., Miczek, K.A., 1993b. Morphine attenuates ultrasonic vocalizations during agonistic encounters in adult rats. Psychopharmacology 111, 367–375.
Vivian, J.A., Miczek, K.A., 1998. Effects of mu and delta opioid agonists and antagonists on affective vocal and reflexive pain responses during social stress in rats. Psychopharmacology 139, 364–375.
Vivian, J.A., Miczek, K.A., 1999. Interactions between social stress and morphine in the periaqueductal gray: effects on affective vocal and reflexive pain responses in rats. Psychopharmacology 146, 153–161.
Vivian, J.A., Farrell, W.J., Sapperstein, S.B., Miczek, K.A., 1994a. Diazepam withdrawal: effects of diazepam and gepirone on acoustic startle-induced 22 kHz ultrasonic vocalizations. Psychopharmacology 114, 101–108.
Vivian, J.A., Weerts, E.M., Miczek, K.A., 1994b. Defeat engenders pentylenetetrazole-appropriate responding in rats: antagonism by midazolam. Psychopharmacology 116, 491–498.
Vivian, J.A., Barros, H.M.T., Manitiu, A., Miczek, K.A., 1997. Ultrasonic vocalizations in rat pups: modulation at the gamma-aminobutyric acid-A receptor complex and the neurosteroid recognition site. J. Pharmacol. Exp. Ther. 282, 318–325.
Votava, M., Krsiak, M., Podhorna, J., Miczek, K.A., 2001. Alprazolam withdrawal and tolerance measured in the social conflict test in mice. Psychopharmacology 157, 123–130.
Wei, E., Way, E.L., 1975. Application of the pellet implantation technique for the assessment of tolerance and physical dependence in the rodent. In: Ehrenpreis, S. (Ed.), Methods in Narcotics Research. Marcel Dekker, New York, pp. 243–259.
Wei, E., Loh, H., Way, E.L., 1973a. Quantitative aspects of precipitated abstinence in morphine-dependent rats. J. Pharmacol. Exp. Ther. 184, 398–403.
Wei, E., Tseng, L.F., Loh, H., Way, E.L., 1973b. Similarity of morphine abstinence signs to thermoregulatory behaviour. Nature 247, 398–400.
Weiss, F., Ciccocioppo, R., Parsons, L.H., Katner, S., Liu, X., Zorrilla, E.P., Valdez, G.R., Ben Shahar, O., Angeletti, S., Richter, R.R., 2001. Compulsive drug-seeking behavior and relapse: neuroadaptation, stress, and conditioning factors. Ann. N. Y. Acad. Sci. 937, 1–26.
Whimbey, A.E., Denenberg, V.H., 1967. Two independent behavioral dimensions in open-field performance. J. Comp. Physiol. Psychol. 63, 500–504.
White, N.R., Prasad, M., Barfield, R.J., Nyby, J.G., 1998. 40- and 70-kHz vocalizations of mice (*Mus musculus*) during copulation. Physiol. Behav. 63, 467–473.
Williams, C.E., Stevens, K.N., 1972. Emotions and speech: some acoustical correlates. J. Acoust. Soc. Am. 52, 1238–1250.
Winslow, J.T., Insel, T.R., 1991. The infant rat separation paradigm: a novel test for novel anxiolytics. Trends Pharmacol. Sci. 12, 402–404.
Wood, D.M., Lal, H., 1987. Anxiogenic properties of cocaine withdrawal. Life Sci. 41, 1431–1436.
Wood, D.M., Laraby, P.R., Lal, H., 1989. A pentylenetetrazol-like stimulus during cocaine withdrawal: blockade by diazepam but not haloperidol. Drug Dev. Res. 16, 269–276.
Woolverton, W.L., Kleven, M.S., 1988. Evidence for cocaine dependence in monkeys following a prolonged period of exposure. Psychopharmacology 94, 288–291.
Yajima, Y., Hayashi, Y., Yoshii, N., 1982. Ambiguus motoneurons discharging closely associated with ultrasonic vocalization in rats. Brain Res. 238, 445–450.
Young, A.M., Thompson, T., 1979. Naloxone effects on schedule-controlled behavior in morphine-pelleted rats. Psychopharmacology 62, 307–314.