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The self-administration of WIN 35,428 and cocaine: comparisons of satiety threshold and elimination half-life in rats

Andrew B. Norman*, William R. Buesing, Mantana K. Norman, Michael R. Tabet, Vladimir L. Tsibulsky

Department of Psychiatry, Division of Neuroscience, College of Medicine, University of Cincinnati, Cincinnati, OH 45267-0559, USA
Department of Pharmacology, Division of Neuroscience, College of Medicine, University of Cincinnati, Cincinnati, OH 45267-0559, USA
Department of Physiology, Division of Neuroscience, College of Medicine, University of Cincinnati, Cincinnati, OH 45267-0559, USA

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Abstract

Rats that self-administered cocaine at unit doses between 0.75 and 12 μmol/kg with mean inter-injection intervals between approximately 2 and 18 min also reliably self-administered the cocaine analogue WIN 35,428 (β-CFT; (−)-3β-(4-fluorophenyl)tropane-2β-carboxylic acid methyl ester) at unit doses between 0.1 and 1.6 μmol/kg with mean intervals between 10 and 116 min. The long inter-injection intervals of WIN 35,428 necessitated sessions of more than 12 h. The inter-injection intervals were regular and proportional to the unit dose, consistent with the satiety threshold model. Analysis of the mean intervals as a function of unit doses generated values for the mean satiety threshold of cocaine and WIN 35,428 of 6.10 and 0.87 μmol/kg, respectively. The mean $t_{1/2}$ for cocaine and WIN 35,428 were 11.1 and 69.4 min, respectively. The approximately 43-fold lower rate of consumption of WIN 35,428 relative to cocaine was a product of the seven-fold greater pharmacodynamic potency and the six-fold greater pharmacokinetic potency.

Keywords: Satiety threshold; Pharmacokinetics; Pharmacodynamics; Cocaine; WIN 35,428

1. Introduction

The maintained self-administration of cocaine is characterized by regular inter-injection intervals and this regularity has been demonstrated to be due to the maintenance of a minimum cocaine level, termed the satiety threshold (Tsibulsky and Norman, 1999). Consistent with this model of the regulation of cocaine self-administration, the measurement of plasma cocaine levels during self-administration sessions has demonstrated that self-administration occurs at a fixed minimum concentration of cocaine (Lau and Sun, 2002) and this may be related to a minimum level of dopamine in specific brain areas (Wise et al., 1995). Furthermore, a minimum maintained level of drug has been proposed to account for the regularity of the self-administration of D-amphetamine (Yokel and Pickens, 1974) and phenethylamine (Cone et al., 1978). According to the satiety threshold model, the increasing inter-injection intervals as a function of unit dose are because the higher cocaine levels take longer to decline back to the satiety threshold. Although the inter-injection intervals of cocaine self-administration are proportional to the unit dose, they are not linearly proportional due to the first order elimination of cocaine (Tsibulsky and Norman, 1999). According to this pharmacokinetic/pharmacodynamic model, it is possible to measure the satiety threshold and the elimination half-life ($t_{1/2}$) of a self-administered drug by measuring the inter-injection intervals as a function of the unit dose of the self-administered drug (Tsibulsky and Norman, 1999).

The structural analogue of cocaine (−)-3β-(4-fluorophenyl)tropane-2β-carboxylic acid methyl ester (WIN 35,428 or β-CFT) has cocaine-like behavioral effects but was more potent than cocaine in a number of behavioral tests including stimulant-induced locomotor activity (Clarke et al., 1973), rotation behavior in rats with unilateral dopaminergic deafferentation of the striatum (Heikkila et al., 1979) and

* Corresponding author. Department of Psychiatry, Division of Neuroscience, College of Medicine, University of Cincinnati, 231 Albert Sabin Way, Cincinnati, OH 45267-0559, USA.
E-mail address: andrew.norman@uc.edu (A.B. Norman).

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cocaine discrimination in rats (Katz et al., 2000) and pigeons (Jarbe, 1981). WIN 35,428 was also self-administered by monkeys and was more potent than cocaine in a second order schedule of self-administration behavior (Spealman et al., 1991). In rats, the locomotor stimulating effects of WIN 35,428 last longer than those of cocaine (Clarke et al., 1973) and the effects of WIN 35,428 on the reinstatement of responding after extinction were also long lasting (Schenk, 2002). These findings suggest that the elimination $t_{1/2}$ of WIN 35,428 may be longer than that of cocaine in rats. Consistent with this suggestion, in mice the elimination $t_{1/2}$ of cocaine was approximately 15 min from plasma and brain (Benuck et al., 1987) and the clearance $t_{1/2}$ of [^{3}H]WIN 35,428 from the striatum was approximately 55 min (Scheffel et al., 1991). Although WIN 35,428 was self-administered by monkeys (Spealman et al., 1991), the present study is the first to measure the maintained self-administration of this cocaine analogue. We report herein that WIN 35,428 is self-administered by rats and that the satiety threshold and elimination $t_{1/2}$ of this compound can be calculated using the satiety threshold model of maintained self-administration.

2. Materials and methods

2.1. Cocaine self-administration training

Five male Sprague–Dawley rats (from SASCO, Wilmington, MA, initial weight 180–200 and 400–500 g over the duration of the studies) were housed individually on a 12-h light–dark cycle (lights on at 6:00 a.m.) and food and water were available ad lib. All studies were conducted in accordance with the Guide for the Care and Use of Laboratory Animals. Rats were surgically implanted with an indwelling catheter into the right jugular vein under halothane anesthesia (Caine et al., 1993). Beginning 6 or 7 days after the surgery, rats were trained to self-administer cocaine HCl using a fixed ratio (FR = 1) schedule with no time out period (TO = 0) after the injection of cocaine is completed. Training at the unit dose of 1.5 μmol/kg cocaine continued until individual rats met the criterion for stable maintained self-administration. This criterion was no significant change of the mean and standard deviation of the inter-injection intervals between five consecutive sessions.

Test chambers (modified chambers from Lafayette Instrument, Lafayette, IN) were each equipped with an active and an inactive lever. Each chamber was situated inside of a laminated wooden compartment (43 × 61 × 35 cm) that provided sound attenuation and was equipped with a house light (7 W). Infusion pumps (model PHM-100, Med Associates, Georgia, VT) were situated outside of the laminated compartments. Computers controlled unconditioned stimuli (drug injection) using a program written in Medstate Notation language (Med Associates). The unit doses of cocaine ranged from 0.75 to 12 μmol/kg **(0.25 to 4.0 mg/kg of cocaine HCC)** and the unit doses of WIN 35,428 ranged from 0.1 to 1.6 μmol/kg **(0.04 to 0.70 mg/kg of WIN 35,428 tartrate)**. The concentrations of the self-administered cocaine and WIN 35,428 solutions were 44 and 2 μmol/ml, respectively. The unit dose of each was regulated by the duration of the injection, which ranged from 2 to 40 s and 6 to 118 s for cocaine and WIN 35,428, respectively. In order to minimize overloading during the initial loading phase of a session, the first four unit doses of cocaine were programmed to be 1.5 μmol/kg and the first nine unit doses of WIN 35,428 were 0.1 μmol/kg. After the self-administration of the initial loading doses, the program switched subsequent doses to the required maintenance dose in random order between sessions.

In order to maintain catheter patency, prior to and after every session, the catheter was flushed with 0.2–0.5 ml of sterile saline containing 10 units/ml heparin. If the catheter was resistant then it was flushed with 0.05–0.1 ml of sterile saline containing 3500 units/ml streptokinase. Catheter patency was evaluated by i.v. administration of short-acting barbiturate methohexital (6 mg/kg, 3 s injection). The catheter was considered patent if administration of methohexital produced a loss of righting reflex within 5 s after the injection was completed and the latency to the recovery of the righting reflex was greater than 120 s. If the catheter was not patent, it was removed and a new catheter was implanted into the left jugular vein.

2.2. Materials

Cocaine HCl and WIN 35,428 tartrate were obtained from Research Triangle Institute (Research Triangle Park, NC) under the National Institute on Drug Abuse drug supply program. The drugs were dissolved in saline solution containing 1 unit/ml of heparin and then passed through a sterile 0.2-μm acetate filter immediately prior to use in the self-administration studies. Heparin sodium was obtained from American Pharmaceutical Partners (Schaumburg, IL). Streptokinase was obtained from Sigma (St. Louis, MO).

2.3. Statistical analysis

The distinct phases of the self-administration session were differentiated on the basis of abrupt and sustained changes in the inter-injection intervals. Only the intervals during the maintenance phase of each session were used to calculate a mean value that was used for further statistical analysis. The dose–response relationship for each rat was estimated on the basis of at least three sessions per dose for cocaine and one session per dose for WIN 35,428. The satiety threshold and $t_{1/2}$ for each drug was estimated as a mean ± S.E.M. of the five values from the individual rats ($n = 5$).

The satiety threshold and $t_{1/2}$ were calculated for each rat using nonlinear regression analysis (SigmaPlot, SPSS) of

the mean inter-injection intervals during the maintenance phase of each session as a function of the unit dose according to the equation:

$$T = \ln(1 + D_U/D_{ST}) \cdot t_{1/2}/\ln(2) \quad (1)$$

where T is the mean inter-injection interval, D_U is the unit dose, D_{ST} is the satiety threshold and $t_{1/2}$ is the elimination half-life of the drug (Tsibulsky and Norman, 1999). The mean ± S.E.M. of the values from the individual rats was then calculated.

3. Results

3.1. Three distinct phases of self-administration sessions for cocaine and WIN 35,428

There are three distinct phases of a typical self-administration session: loading, maintenance, and extinction (Norman and Tsibulsky, 2001). At the lower unit doses, an initial series of self-injections with short intervals were observed for WIN 35,428 (Fig. 1). This loading phase was followed by an abrupt increase in the inter-injection intervals at the same unit dose indicating the maintenance phase of the session. At all unit doses of WIN 35,428, after the initial loading phase, there was typically a single relatively long interval after which the inter-injection intervals were stable while WIN 35,428 was available. This phenomenon was also observed at higher unit doses of cocaine. Therefore, in order to minimize this overloading, especially at higher unit doses, the first four unit doses of cocaine (see Fig. 2A) and the first nine unit doses of WIN 35,428 (see Fig. 2B) were 1.5 and 0.1 μmol/kg, respectively. After the termination of access to both cocaine and WIN 35,428, there was an abrupt decrease in the inter-response intervals. This increase in the rate of lever pressing represented the extinction phase of the session, which typically lasted for approximately 30–50 min for cocaine and approximately 6–8 h for WIN 35,428.

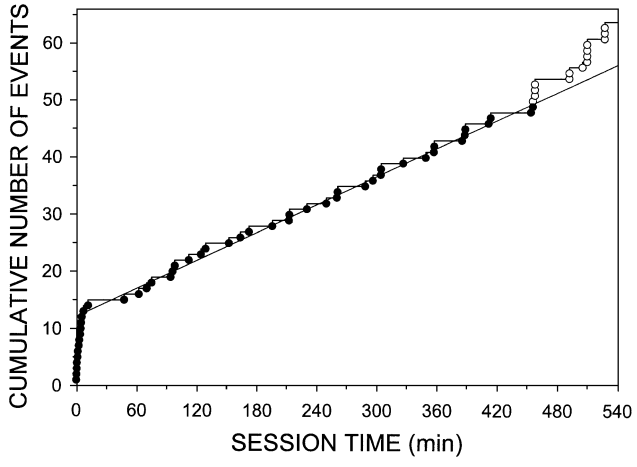

Fig. 1. A cumulative event record from a representative self-administration session of WIN 35,428. The unit dose of WIN 35,428 was 0.1 μmol/kg under an FR = 1, no time out schedule in a rat previously trained to reliably self-administer cocaine. Each vertical increment represents each self-administration during the loading and maintenance phases of the session (filled circles), or a lever press during the extinction phase of the session (open circles) and the horizontal distance between these events represents the inter-event interval. The mean ± S.E.M. inter-injection intervals during the initial loading phase and the maintenance phase of this session were 26 ± 4 s (n = 14 injections) and 719 ± 104 s (n = 34 injections), respectively. The lack of systematic deviation of the intervals during the maintenance phase of the session from the linear regression line demonstrates the regularity of self-administration. The extinction phase of the session (open circles) lasted for 167 min and was truncated for clarity.

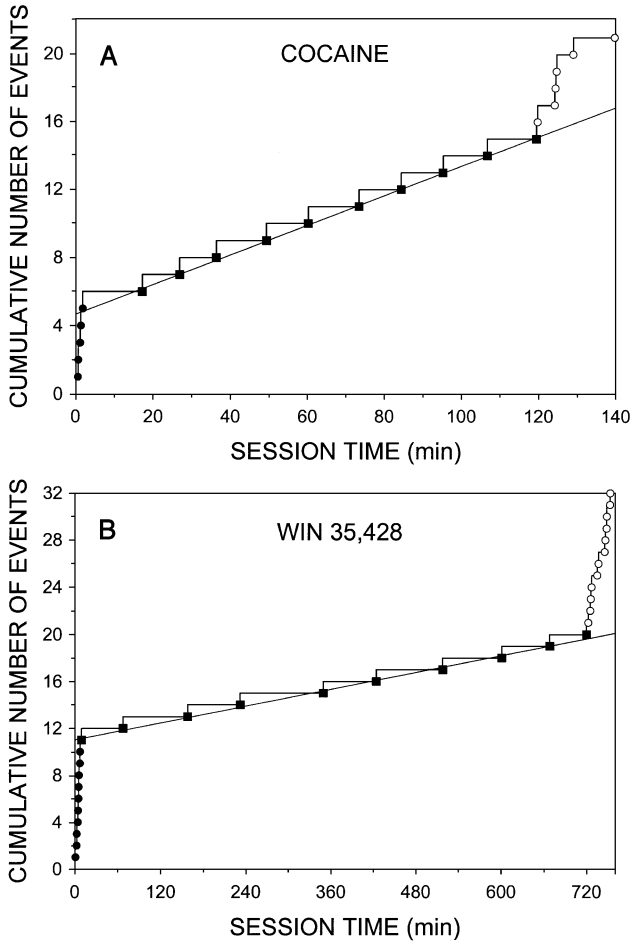

Fig. 2. Cumulative event records from representative self-administration sessions of cocaine (A) and WIN 35,428 (B) from the same rat. In these sessions, the unit doses of cocaine and WIN 35,428 were 6.0 and 0.8 μmol/kg, respectively, which are close to the value of the satiety threshold for each respective drug. The unit doses for cocaine and WIN 35,428 during the initial loading phase of the sessions (filled circles) were 1.5 and 0.1 μmol/kg for cocaine and WIN 35,428, respectively. For the maintenance phase of each session (filled squares), the mean ± S.E.M. inter-injection intervals were 682 ± 27 s (n = 9 injections) and 4737 ± 400 s (n = 9 injections) for cocaine (panel A) and WIN 35,428 (panel B), respectively. The lack of systematic deviation of the intervals from the linear regression lines during the maintenance phases of the sessions demonstrates the regularity of the self-administration of both cocaine and WIN 35,428. The extinction phase (open circles) was truncated for clarity.

3.2. Drug consumption during the maintenance phase

The inter-injection intervals during the maintained self-administration of both cocaine (Fig. 2A) and WIN 35,428 (Fig. 2B) were regular during a session. Furthermore, the mean inter-injection intervals increased as a function of the unit dose for both cocaine (Fig. 3A) and WIN 35,428 (Fig. 3B). However, for both self-administered drugs, the function was not linear. Therefore, the rate of consumption of both cocaine and WIN 35,428 increased with increasing unit dose. The mean ± S.E.M. rate of consumption of cocaine ranged from 25.5 ± 1.6 μmol/kg/h at a unit dose of 0.75 μmol/kg to 41.6 ± 2.0 μmol/kg/h at a unit dose of 12 μmol/kg, a significant increase in consumption at the higher unit dose ($P < 0.01$, paired t-test). In these same animals, the mean ± S.E.M. rate of consumption of WIN 35,428 ranged from 0.44 ± 0.02 μmol/kg/h at a unit dose of 0.1 μmol/kg to 0.98 ± 0.10 μmol/kg/h at a unit dose of 1.6 μmol/kg, a significant increase in consumption at the higher unit dose ($P < 0.001$, paired t-test). Therefore, during the maintenance phase of the self-administration sessions, the rate of consumption of WIN 35,428 was between 42- and 58-fold lower than the rate of consumption of cocaine over the ranges of unit doses used.

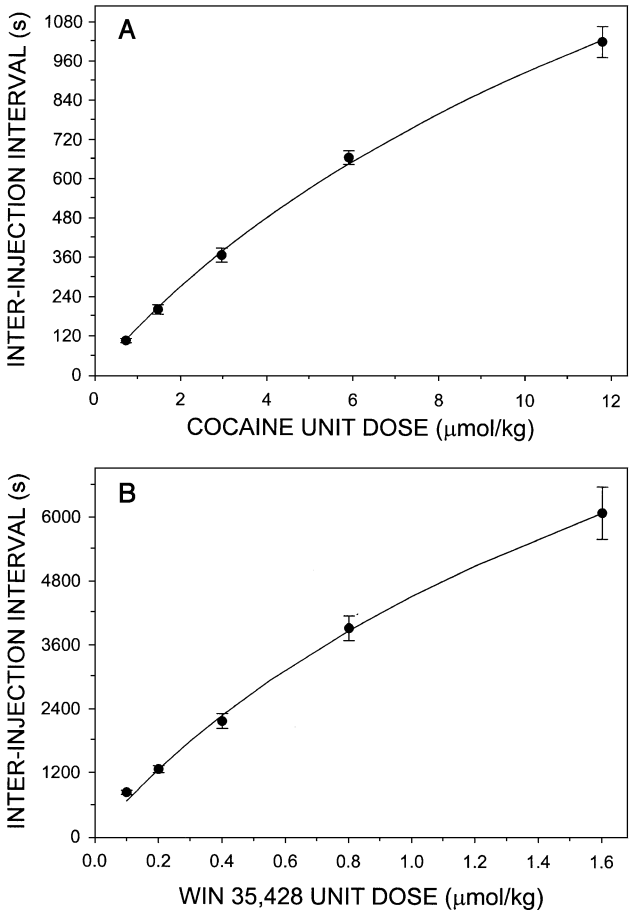

Fig. 3. Inter-injection intervals as a function of the unit dose of cocaine (A) and WIN 35,428 (B). Symbols represent the mean ± S.E.M. inter-injection intervals of five rats. The regression lines represent the best fit through the data points from nonlinear regression analysis according to Eq. (1). The correlation coefficients were 0.999 and 0.998 for cocaine and WIN 35,428, respectively. Based on the mean inter-injection intervals of five rats, the calculated satiety thresholds for cocaine and WIN 35,428 were 6.03 and 0.75 μmol/kg, respectively. The calculated $t_{1/2}$ for cocaine and WIN 35,428 were 11.0 and 61.9 min, respectively.

3.3. The satiety threshold and $t_{1/2}$ for cocaine and WIN 35,428

Nonlinear regression analysis of the inter-injection intervals as a function of unit dose of drug according to Eq. (1) generated values for satiety threshold and $t_{1/2}$ that provided the best fit to the data. As shown in Fig. 3A and B, there was no statistically significant difference ($r^2 > 0.99$) between a mathematical model based on Eq. (1) and the experimentally determined data points. The nonlinear regression analysis presented in Fig. 3A and B was performed on the group mean data. When the data from each rat were analyzed individually, the mean ± S.E.M. satiety thresholds for cocaine and WIN 35,428 were 6.10 ± 0.43 and 0.87 ± 0.20 μmol/kg, respectively. The mean ± S.E.M. $t_{1/2}$ for cocaine and WIN 35,428 were 11.1 ± 0.7 and 69.4 ± 12.9 min, respectively. Therefore, the mean satiety threshold for cocaine in this group of five rats was approximately seven-fold higher than the mean satiety threshold for WIN 35,428 while the mean $t_{1/2}$ for cocaine was approximately six-fold shorter than the mean $t_{1/2}$ for WIN 35,428.

4. Discussion

4.1. The regulation of both cocaine and WIN 35,428 self-administration is consistent with the satiety threshold model

The pattern of self-administration of WIN 35,428 was similar to that of cocaine. The initial loading phase that was observed during the self-administration of WIN 35,428 was a similar phenomenon to that observed during the self-administration of cocaine (Norman and Tsibulsky, 2001). Following the abrupt increase, the inter-injection intervals of both drugs were then regular. This is consistent with the satiety threshold model of the regulation of maintained self-administration where the regularity of intervals is due to a minimum maintained level of drug that is constant during the maintenance phase of the self-administration session (Tsibulsky and Norman, 1999). Furthermore, the inter-injection intervals increased as a function of the unit dose. This is because it takes longer for the higher drug levels to decline back to the satiety threshold. The nonlinearity of the inter-injection intervals of cocaine and WIN 35,428 as a function of the unit dose is consistent with the elimination of both drugs by first-order processes.

Consistency with the satiety threshold model of self-administration allowed nonlinear regression analysis according to Eq. (1) to be applied to the dose–response curves. The satiety thresholds for WIN 35,428 and cocaine represent pharmacodynamically equipotent levels of these drugs with WIN 35,428 being seven-fold more potent than cocaine.

4.2. The pharmacokinetics of WIN 35,428

The duration of a defined magnitude of response is a measure of the pharmacokinetic potency of a drug. As the calculated $t_{1/2}$ of WIN 35,428 was approximately six-fold longer than the $t_{1/2}$ of cocaine, then WIN 35,428 has six-fold greater pharmacokinetic potency relative to cocaine. Although WIN 35,428 has no benzoyl ester moiety and would not be expected to be a substrate for the butyrylcholinesterase that metabolizes cocaine to ecgonine methyl ester, WIN 35,428 does retain the same methyl ester moiety as cocaine. Benzoylecgonine, formed by the enzymatic hydrolysis of the methyl ester, is the major metabolite of cocaine after i.v. administration in the rat (Booze et al., 1997). Therefore, it may be expected that WIN 35,428 would be metabolized with a similar rate constant as cocaine. If the tissue methyl esterase(s) (Dean et al., 1995) are the major metabolic pathway for the degradation of cocaine in the rat (Warner and Norman, 2000), it is likely that the greater pharmacokinetic potency of WIN 35,428 is due to it being a poor substrate for these enzymes.

[^{3}H]WIN 35,428 was reported to have a clearance $t_{1/2}$ of approximately 55 min from the striatum after a single i.v. injection in mice (Scheffel et al., 1991). This is not inconsistent with our finding of an approximately 69-min elimination $t_{1/2}$ of WIN 35,428 from the effect compartment in rats. The biodistribution of WIN 35,428 has been studied in vivo in monkeys using positron emission tomography (PET) imaging (Wong et al., 1993) and ex vivo in monkeys (Kaufman and Madras, 1992) and in rats (Haaparanta et al., 1996). Theoretically, these techniques can also provide pharmacokinetic data for the radioligands. However, the short decay half-life of the ^{11}C radioisotope used in the in vivo PET imaging studies, as well as the potential presence of labeled but inactive metabolites, complicate the measurement of the pharmacokinetics of radioligands. However, the detection of ^{18}F in the striatum of rats at 2 and 4 h after an injection of tracer amounts of [^{18}F]WIN 35,428 (Haaparanta et al., 1996) is consistent with a relatively long $t_{1/2}$ of this drug.

4.3. The pharmacodynamics of WIN 35,428

The level of drug required to produce a defined magnitude of response is a measure of the pharmacodynamic potency of a drug. As the level of WIN 35,428 required to induce satiety was seven-fold lower than the level of cocaine required to induce satiety, then WIN 35,428 has seven-fold greater pharmacodynamic potency relative to cocaine. The satiety thresholds of drugs that act via the same pharmacological substrates should reflect their affinities for the sites mediating the satiety response. The self-administration of cocaine and cocaine-mimetic drugs may be mediated by their interactions with the dopamine transporter (Ritz et al., 1987) and/or the serotonin transporter (Walsh and Cunningham, 1997). Cocaine and WIN 35,428 have approximately equal selectivity for the dopamine and serotonin transporters. However, the affinities of cocaine for these transporters are approximately six- to eight-fold lower than those of WIN 35,428, with dissociation constants in the range of 300–400 and 40–60 nM, respectively (Reith et al., 1986; Ritz et al., 1987; Rothman et al., 1994; Carroll et al., 1995; Meltzer et al., 2002). Therefore, the correspondence between the relative potency of WIN 35,428 and cocaine, as measured by their satiety thresholds in vivo and transporter binding in vitro, is consistent with the involvement of the dopamine transporter and/or the serotonin transporter in the regulation of the satiety response in rats.

4.4. The relative potencies of drugs defined by the rate of consumption

The rate of consumption of a drug is a measure of its potency to maintain the satiety response. This measure is a product of a drug's pharmacodynamic and pharmacokinetic potencies. The rate of consumption of a drug is inversely proportional to its potency at maintaining the satiety response. However, the rate of consumption of cocaine and WIN 35,428 increased as a function of the unit dose, demonstrating that the higher doses are less potent at maintaining the same magnitude of response (i.e. satiety). It is unlikely that the satiety threshold or $t_{1/2}$ changes as a function of the unit dose, and the increase in consumption can be explained by first order elimination kinetics (Tsibulsky and Norman, 1999). Because the rate of consumption varies with unit dose, comparing the relative potencies of different drugs must use a standardized unit dose. A unit dose equal to the satiety threshold for each drug represents a convenient standard unit dose for comparison purposes. The rate of consumption during maintained self-administration of cocaine at a unit dose of 6.0 μmol/kg and of WIN 35,428 at 0.8 μmol/kg was 31.60 and 0.73 μmol/kg/h, respectively. These unit doses are close to the respective satiety thresholds and are therefore approximately equipotent. The 43-fold higher potency of WIN 35,428 at maintaining the satiety response is the product of two distinct components: seven-fold lower levels of WIN 35,428 are required to maintain satiety, and when administered, it takes six-fold longer for WIN 35,428 levels to decline back to the satiety threshold. Therefore, relative to cocaine, a 43-fold lower infusion rate of WIN 35,428 would be required to maintain the drug levels at their respective satiety thresholds.

4.5. Long sessions are required to measure the inter-injection intervals for WIN 35,428

At the highest unit dose of WIN 35,428 used in this study, the mean inter-injection intervals during maintained self-administration were almost 2 h. Therefore, long sessions are required in order to obtain a reliable estimate of the mean inter-injection intervals. Indeed, once the loading phase is complete, it takes at least 11 h to measure just nine intervals at a unit dose of 0.8 μmol/kg. Obviously, the duration of the maintenance phase of a self-administration session should be proportional to the $t_{1/2}$ of the drug. Another structural analogue of cocaine, β-CIT (or RTI-55; (−)-3β-(4-iodophenyl)tropane-2β-carboxylic acid methyl ester) identical to WIN 35,428 except having an iodine atom in place of the fluorine, may also have a comparably long $t_{1/2}$. β-CIT was also self-administered by monkeys previously trained to self-administer cocaine (Weed et al., 1995). β-CIT was more potent than cocaine, had a long duration of action and the responding was reported to be concentrated at the beginning of 1-h sessions (Weed et al., 1995). This latter finding is consistent with the loading phase of the session. These short inter-injection intervals during the loading phase clearly demonstrate that the drug is self-administered, but provide no pharmacokinetic data and only semi-quantitative pharmacodynamic data.

The relatively long inter-injection intervals observed with WIN 35,428 were also observed with certain opiates. The self-administration of the opioid receptor agonist l-α-acetylmethadol by rats trained to self-administer morphine was characterized by inter-injection intervals of approximately 8 h (Moreton et al., 1976; Young and Khazan, 1987). L-α-Acetylmethadol and its active metabolites have long half-lives and are potent opioid receptor agonists.

It has been suggested that substitution medications for cocaine dependence should have a long duration of action. It should be expected that the maintenance phase of self-administration sessions of drugs with long half-lives will require very long sessions. For example, if a drug had a $t_{1/2}$ of 12 h, then at a unit dose equivalent to the satiety threshold of the drug, the inter-injection intervals during the maintenance phase of the session would also be 12 h (see Eq. (1)). To measure 10 intervals at this unit dose would take 5 days.

4.6. Summary

The regularity of the maintained self-administration of WIN 35,428 and the proportionality of the inter-injection intervals with the unit dose are consistent with the satiety threshold model previously developed to explain cocaine self-administration. The nonlinearity of the inter-injection intervals as a function of unit dose is consistent with the first order elimination of WIN 35,428. The approximately 43-fold lower rate of consumption of WIN 35,428 relative to that of cocaine was the product of WIN 35,428's 7-fold greater pharmacodynamic potency and 6-fold longer $t_{1/2}$.

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