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ORIGINAL INVESTIGATION

Ketamine self-administration in the rat: evidence for a critical role of setting

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Abstract
Rationale The abuse of ketamine has been reported to be on the rise over the past 15 years, but its abuse appears to be limited almost exclusively to the context of music and dance settings, indicating a major role of context in modulating its reinforcing effects. We have previously reported that amphetamine, cocaine, and heroin self-administration (SA) in the rat are differentially influenced by the setting in which testing takes place. The aim of the present study is to extend this pre-clinical model to ketamine.
Materials and methods Independent groups of rats with intravenous catheters were given the possibility to self-administer different doses of ketamine (125, 250, and 500 μg/kg per infusion) under two environmental conditions. Some animals were housed in the SA chambers (resident rats) whereas other rats were transported to the SA chambers only for the test sessions (non-resident rats). After training, within-subject dose effect curves (125, 250, 500, and 1,000 μg/kg per infusion) and break-point (during a progressive ratio session) were calculated.
Results Non-resident rats readily acquired ketamine self-administration. In contrast, resident rats self-administered only the highest dose of ketamine (500 μg/kg), but still four times less than non-resident rats (11.0±6.0 vs 44.4±5.2 infusions during the last training session). No significant differences in break-point were found during the progressive ratio session.
Conclusions The present study confirms at a preclinical level the importance of setting for ketamine SA and further validates a previously described animal model of drug–environment interaction.

Keywords Ketamine · Club drugs · Reward · Addiction · Drug abuse · Self-administration · Context · Setting

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Introduction

Clinical and preclinical evidence indicates that environmental context plays an important role in modulating individual responsiveness to addictive drugs (for a review, see Caprioli et al. 2007a). The role of setting appears to be particularly important for "club drugs" such as ketamine, a general anesthetic whose recreational use is being reported ever more frequently in different countries and whose abuse appears to be limited mostly to raves and "club" settings (Curran and Morgan 2000; Joe Laidler 2005; Degenhardt and Dunn 2008).

We have recently developed an animal model to study under laboratory conditions the role of setting on drug taking (Caprioli et al. 2007a). Some rats are transferred to the self-administration (SA) chambers immediately before the SA sessions (non-resident rats), whereas other animals were kept at all times in the SA chambers (resident rats). We found that setting modulates SA in different manners

depending on the drug. Psychostimulant drugs, such as cocaine and amphetamine, were self-administered more by non-resident rats than by resident rats, while the opposite occurred with heroin SA (Caprioli et al. 2007b, 2008; Celentano et al. 2009). When rats were given the choice between cocaine and heroin, their drug preferences also turned out to be influenced by the setting. Most resident rats in fact chose heroin over cocaine, whereas most non-resident rats chose cocaine over heroin (Caprioli et al. 2009). These surprising results indicate an unforeseen dissociation between psychostimulant and opioid reward. The heuristic relevance of our model is indicated by the results of a translational study in which we investigated the ambience selected by human co-abusers to inject heroin and cocaine intravenously. Most addicts in fact reported using heroin at home and cocaine outside the home (Caprioli et al. 2009).

We have hypothesized that the setting affects drug taking by providing an ecological backdrop against which drug effects are rated as more or less adaptive (Caprioli et al. 2009). The sedative, inward-looking effects of heroin, for example, would be experienced as suitable to a safe, non-challenging, home environment, whereas the sympathomimetic, activating, performance-enhancing effects of cocaine would be more appropriate to arousing, exciting contexts. We hypothesize here that some of the effects of ketamine (tachycardia, increased blood pressure, hyperexcitability, agitation, and hallucinations) would be more appropriate to a non-home than to a home environment (as in the case of our non-resident vs resident rats). Furthermore, although the pharmacological profile of ketamine is very complex and quite different from that of psychostimulant and opioid drugs, some of its actions are more similar to that of the former than to the latter. Ketamine, for example, has been reported to increase dopamine efflux and to reduce dopamine uptake in the nucleus accumbens (Hancock and Stamford 1999). These considerations and ketamine's popularity among club-goers lead us to predict that its intake would be greater in non-resident than in resident rats. Thus, the goal of the present study is to investigate the role of drug-taking context for ketamine SA in the rat, using the model outlined above.

Materials and methods

Animals

The study was conducted using 46 male Sprague–Dawley rats (Harlan Italy, San Pietro al Natisone, Italy) weighing 275 g at their arrival in the laboratory. Notice that one additional rat was tested but was excluded from the analyses because it failed the catheter patency test described below. Throughout the experiment, all rats were housed and tested in the same dedicated temperature- and humidity-controlled rooms, with free access to food and water (except during the test sessions) under a 14-h dark/10-h light cycle (lights off at 0700 h). After their arrival, the rats were housed two per cage for 7–10 days before the surgery. After the surgery, the rats were housed individually (see "Procedures" section). All procedures were in accordance with the Italian Law on Animal Research (DLGS 116/92) and with the guidelines for the care and use of laboratory animals issued by Italian Ministry of Health.

Surgery

The IV catheter consisted of 10.5 cm of silicone tubing (0.37-mm inner diameter, 0.94-mm outer diameter) sheathed, at 3.4 cm from its proximal end, by a 5-mm length of heat-shrink tubing. On the day of surgery, the rats received an intraperitoneal (ip) injection of 2.33 mg of xylazine hydrochloride (Rompun®, Bayer HealthCare) and an intramuscular injection of 14,000 IU of benzylpenicillin (Fournier Pharma, S. Palomba, Italy). The rats were then anesthetized with an ip injection of 0.56 ml/kg of Zoletil 100® (Virbac, Carros, France), containing tiletamine (50 mg/ml) and zolazepam (50 mg/ml). Using standard surgical procedures, the catheter was inserted into the right jugular vein, so as to reach the right atrium with its proximal end, and was then secured to the surrounding soft tissues with silk thread. The distal end of the catheter was passed subcutaneously in front of the left shoulder, externalized through a small incision at the nape of the neck, and connected to an L-shaped 22-gauge cannula. The cannula was then secured to the rat's skull using dental cement and stainless steel screws. After surgery, the rats were given 0.7 ml of gentamycin solution (40 mg/ml; Schering-Plough, Milan, Italy) in a single iv bolus. Catheters were flushed daily (at 1800 h) with 0.1 ml of a sterile saline solution containing 0.3 mg of gentamycin and 12.5 IU heparin (Marvecs Services, Agrate Brianza, Italy).

Apparatus

The apparatus consisted of SA chambers (28.5-cm length, 27-cm width, and 32-cm height) made of transparent plastic (front and rear walls), aluminum (sidewalls and ceiling), and stainless steel (grid floor). Plastic trays covered with pinewood shaving were placed under the grid floors. Each chamber was equipped with two retractable levers, positioned on the left-hand wall 12.5 cm apart and 9 cm above the floor, three cue lights (red, yellow, and green), positioned above each lever, and a counterbalanced arm holding a liquid swivel. The SA chambers were placed within sound-and light-attenuating cubicles. Each cage was

connected via an electronic interface to a syringe pump (Razel Scientific Instruments, St. Albans, VT, USA) and to a programmable logic controller (PLC; Allen Bradley, Milwaukee, WI, USA), in turn connected to a PC. Chambers, accessories, and electronic interfaces were purchased from ESATEL S.r.l. (Rome, Italy), and custom-developed control software from Aries Sistemi S.r.l. (Rome, Italy). The infusion line consisted of a length of silastic tubing protected by a stainless steel spring and connected (through the liquid swivel and another length of silastic tubing) to a syringe positioned on the pump (which was programmed to work at an infusion rate of 10 μl/s).

Procedures

After the surgery, the rats were assigned to one of two testing conditions: resident vs non-resident. The rats in the resident groups were housed in the SA chambers where they remained for the entire duration of the experiment. Four hours before the start of each session, the syringe pumps were activated, so as to fill the infusion lines, which were then connected to the catheters. During the 60 s preceding the start of each SA session, food and water were removed from the cage, and the infusion pumps were activated for 4 s, so as to fill the catheters (20 μl) and provide an initial priming infusion of 20 μl. Self-administered drug infusions and further primings consisted of 40 μl of drug solution and were delivered over a period of 4 s. During the SA sessions, the doors of the cubicles were kept closed.

Non-resident rats were housed in transparent plastic cages (40-cm length, 24.5-cm width, and 18-cm height) with stainless steel tops and flat bottoms covered with ground corncob bedding. Immediately before the start of each SA session, non-resident rats were transferred to the SA chambers, and their catheters were connected to infusion lines filled with the appropriate drug solution. All other testing procedures were identical to those described above for the resident rats (including the absence of food or water). At the end of the session, non-resident rats were returned to their home cages.

All test sessions lasted 3 h and took place during the dark phase, between 0900 and 1700 h, 7 days a week.

Sessions 1–11

Testing began 1 week after the surgery. At the start of each session, the two levers were extended and remained extended for the entire duration of the session (except during the time-out periods; see below). Only one of the two levers was active (that is, it triggered, upon completion of the task, an infusion of ketamine), whereas the other lever had no direct consequences on ketamine infusion. Within each group, left and right levers were counterbalanced for the active vs inactive status.

The number of consecutive responses required to obtain, on a fixed ratio (FR) schedule, a single infusion was raised from FR1 (sessions 1–4) to FR2 (sessions 5–7) and then to FR5 (sessions 8–11). Upon completion of the task, both levers retracted and were extended again after 40 s (time-out). The three light above the active lever were on when the lever was extended and off when the lever was retracted. No other light cue was provided. Pressing on the inactive lever produced no lever retraction but did reset the counter of the active lever.

On the first test session, all animals were placed with their forepaws on the active lever, so as to trigger a priming infusion. Priming infusions were administered again at times 60 and 120 min to animals that had not spontaneously self-administered at least one infusion during time periods 0–60 and 60–120 min, respectively. On sessions 2–7, priming infusions were administered at times 5, 60, and 120 min to animals that had not spontaneously self-administered at least one infusion during time periods 0–5, 5–60, and 60–120 min, respectively. On sessions 8–11, a priming infusion was administered at time 5 min to animals that had not spontaneously self-administered at least one infusion. During training, all rats but one received primings. On average, resident rats received 1.1 primings per session (1.14, 1.04, and 1.12 for groups 125, 250, and 500 μg/kg, respectively) and non-resident rats 0.62 primings per session (0.62, 0.61, and 0.34, for groups 125, 250, and 500 μg/kg, respectively).

Separate experiments were conducted to investigate, in independent groups, the acquisition of SA for the following doses of ketamine (μg/kg dissolved in 40 μl of sterile saline): 125 (N=6 for the resident group; N=6 for the non-resident group), 250 (N=10 for the resident group; N=9 for the non-resident group), and 500 (N=8 for the resident group; N=7 for the non-resident group). These doses of ketamine were selected on the basis of a preliminary experiment conducted in our laboratory (notice that they are in the range of those used by Collins and Woods 2007). During sessions 1–11, the rats were allowed to self-administer a maximum of 50 infusions of ketamine to minimize the risk of overdosing.

Sessions 12–15 (dose–effect curve)

During sessions 12–14, the rats were given the possibility to self-administer (following a Latin square design), three additional doses of ketamine besides that self-administered on sessions 1–7. On session 15 the rats were returned to the initial dose of ketamine. No drug priming was administered at the start of this session. Sessions 12–15 were conducted on an FR5 schedule of reinforcement.

Session 16 (break-point)

On session 12, the rats underwent a progressive ratio procedure during which the number of responses required to obtain a single infusion (of the same drug solution used during training) was increased within the session according to the following progression: 5, 10, 20, 30, 50, 70, 100, 150, 200, 300, 500, and so on. The break-point (defined as the highest ratio reached during the session) is usually taken to indicate the motivation for drug taking. No drug priming was administered at the start of this session.

Summary of group differences between resident and non-resident rats

(1) The SA chambers were physically identical for all rats but for some animals they were also the home environment (resident group) whereas for other animals it represented a distinct and, at least initially, novel environment (non-resident group). (2) During testing, the SA chambers contained no food or water. The rest of time the animals had free access to food and water. (3) The distance traveled by non-resident rats during the transfer to the SA chamber was about 1 m (all animals were kept in the same dedicated testing rooms for the entire duration of the experiments and therefore there was no transport from one room to another). (4) Immediately before the start of each session resident rats were briefly handled to remove food and water from the chamber. 5) When necessary, both resident and non-resident rats were briefly handled to deliver a priming infusion. (6) All other husbandry routines were identical in the two groups.

Catheter patency test

After the last test session all rats underwent a catheter patency test consisting in the administration 40 mg/kg of thiopental sodium in a single iv bolus. One rat failed the catheter patency test, that is, it did not became ataxic within 5 s after thiopental.

Data analysis and statistics

Priming infusions were subtracted from the raw data. Lever pressing data during sessions 1–11 were analyzed using a four-way ANOVA for factors setting (two levels: resident vs non-resident) and training dose (three levels: 125, 250, and 500 μg/kg), and with repeated measures on factors session (11 levels) and lever (two levels: active vs inactive). Infusion data during sessions 1–11 were analyzed using a three-way ANOVA for factors setting and training dose and with repeated measures on the factor session.

The mean number of infusions and mean intake of ketamine during the training sessions conducted on FR5 (sessions 8–11) were calculated to summarize dose–effect relationships for the acquisition of SA. However, these data were analyzed using three-way ANOVAs for factors setting and training dose, with repeated measures on factors session (four levels).

The within-subject dose–effect data (sessions 12–15) were analyzed using three way ANOVAs for factors setting and training dose, with repeated measures on factor dose (four levels: 125, 250, 500, and 1,000 μg/kg).

Mann–Whitney tests were used to analyze break-point data (session 16).

Results

Figure 1 illustrates the number of presses on the active vs the inactive lever during the 11 sessions of the training phase. The rats acquired ketamine SA as indicated by the fact that they pressed more on the active than on the inactive lever and increased the rate of pressing on the active lever as a function of FR. Indeed, the four-way ANOVA yielded significant effects of session [$F(10,400)=16.94$, $p<0.0001$] and lever [$F(1,40)=43.95$, $p<0.0001$], with session × training dose [$F(20,400)=3.07$, $p<0.0001$] and lever × training dose [$F(2,40)=5.03$, $p=0.011$] interactions. However, the reinforcing effect of ketamine was much greater in the non-resident that in resident rats, as indicated by a significant effect of setting [$F(1,40)=19.4$, $p<0.0001$] and by setting × session [$F(10,400)=9.88$, $p<0.0001$] and setting × lever [$F(1,40)=20.93$, $p<0.0001$] interactions. Non-resident rats acquired ketamine SA at all training doses. In contrast, resident rats self-administered only the highest dose of ketamine (500 μg/kg) but still four times less than non-resident rats.

Figure 2, illustrates the number of infusions self-administered during sessions 1–11. A tree-way ANOVA (with repeated measures on the factor session) yielded a significant effect of session [$F(10,400)=4.77$, $p<0.0001$] and of setting [$F(1,40)=21.96$, $p<0.0001$], whereas the effect of training dose only approached significance ($p=0.08$). There were also session × training dose [$F(20,400)=2.66$, $p<0.0001$] and session × setting [$F(10,400)=3.25$, $p<0.0001$] interactions, but no session × training dose × setting or setting × training dose interactions ($p=0.16$ and $p=0.36$, respectively).

Figure 3 illustrates the mean number of infusions (left panel) and mean intake (right panel) during the training sessions conducted on FR5. Although each symbol refers to the mean values for sessions 8–11, the data were analyzed using three-way ANOVAs (with repeated measures on the factor session). The ANOVA conducted on the infusion

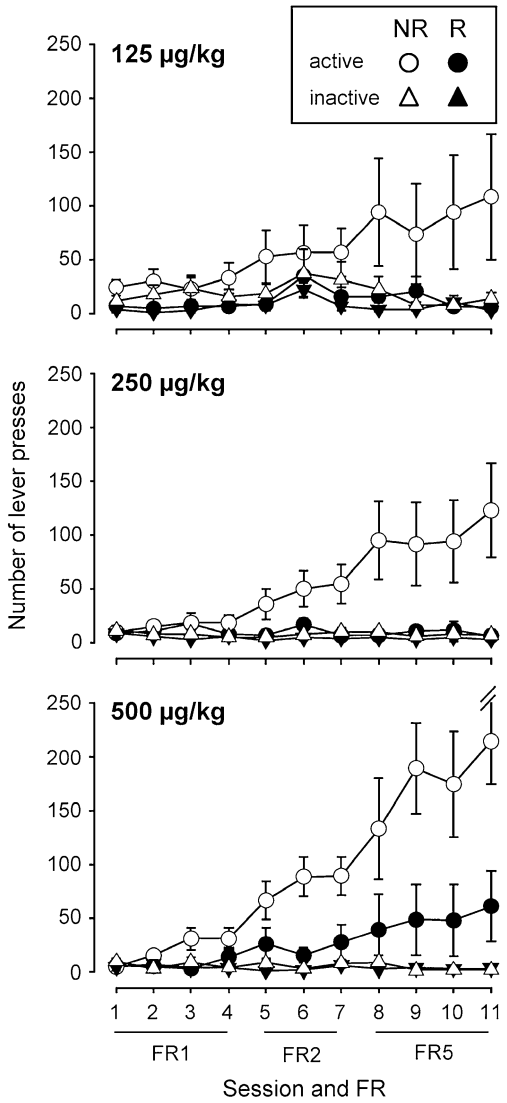

Fig. 1 Mean number (±SEM) of lever presses on the active and inactive levers for rats self-administering ketamine under resident vs non-resident conditions (see text). Independent groups of rats self-administered 125, 250, or 500 µg/kg per infusion (*top*, *middle*, and *bottom panels*, respectively). The FR was progressively increased from 1 (sessions 1–4) to 2 (sessions 5–7) to 5 (sessions 8–11)

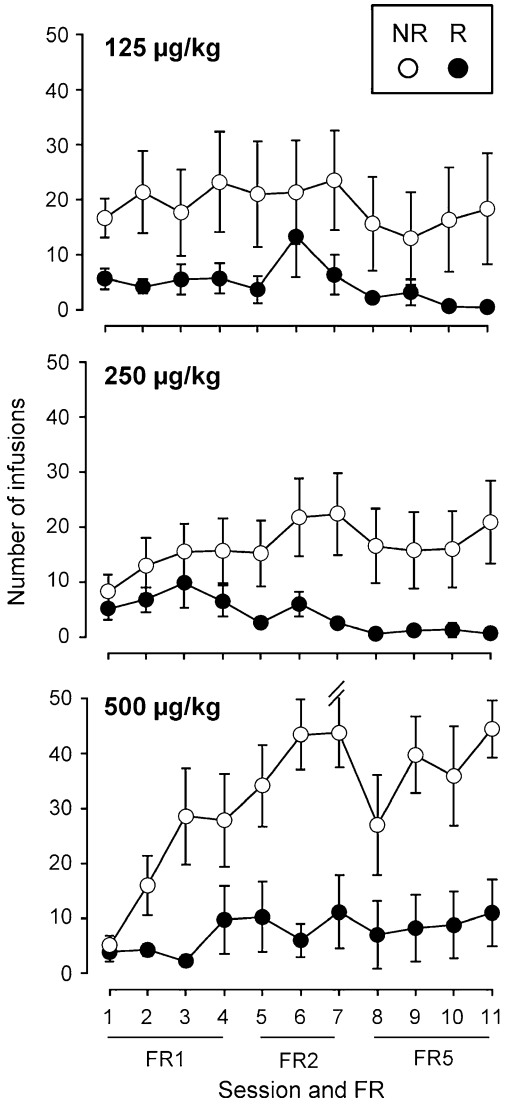

Fig. 2 Mean number (±SEM) of ketamine infusions for the same rats in Fig. 1

data indicated significant effects of setting [$F(1,40)>19.91$, $p<0.0001$] and training dose [$F(2,40)=4.5$, $p=0.017$], but no setting × training dose interaction ($p=0.40$). There was no effect of session ($p=0.12$) nor session × setting ($p=0.26$), session × training dose ($p=0.40$), session × setting × training dose ($p=0.73$) interaction. The ANOVA of intake data indicated a significant effect of setting [$F(1,40)>19.93$, $p<0.0001$] and training dose [$F(2,40)=19.08$, $p<0.0001$], and a setting × training dose interaction [$F(2,40)>6.24$, $p<0.004$]. There was no effect of session ($p=0.11$) nor session × setting ($p=0.40$), session × training dose ($p=0.17$), session × setting × training dose ($p=0.65$) interactions.

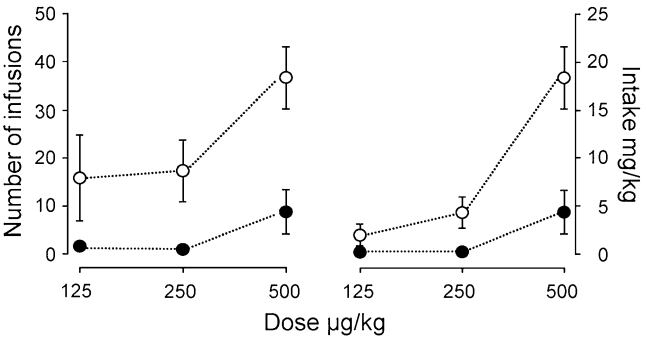

Fig. 3 Dose effect curve for the acquisition of ketamine self-administration. Each *symbol* indicates the mean number (±SEM) of infusions or the mean intake (±SEM) of ketamine (*left* and *right panels*, respectively) on a FR5 schedule of reinforcement (i.e., mean values calculated for sessions 8–11)

Figure 4 illustrates the within-subject dose effect curves for infusions and intake calculated on sessions 12–15. The three-way ANOVA on infusion data (with repeated measures on the factor dose) indicated significant effects of setting [$F(1,40)=13.34$, $p<0.001$] and dose [$F(3,120)=6.34$, $p<0.001$], but not of training dose ($p=0.09$). There were no significant setting × training dose ($p=0.62$), setting × dose ($p=0.14$), training dose × dose ($p=0.66$), setting × training dose × dose ($p=0.84$) interactions. The three-way ANOVA on intake data (with repeated measures on the factor dose) indicated significant effects of setting [$F(1,40)=12.69$, $p<0.001$] and dose [$F(3,120)=19.85$, $p<0.0001$], with significant setting × dose [$F(3,120)=7.83$, $p<0.001$] and training dose × dose [$F(6,120)=2.43$, $p<0.03$] interactions. There was a trend for a significant effect of training dose [($F(2,40)=2.89$, $p=0.067$], but no setting × training dose ($p=0.73$) or setting × training dose × dose ($p=0.90$) interactions.

During the progressive ratio session, there was a trend for non-resident rats to lever press more than resident rats but the Mann–Whitney test yielded no significant group differences at any dose: 125 μg/kg (54.3±27.5 vs 31.3±27.5; $p=0.11$), 250 μg/kg (25.1±22.4 vs 20.7±21.3; $p=0.16$), 500 μg/kg (147.4±25.4 vs 87.2±23.8; $p=0.16$).

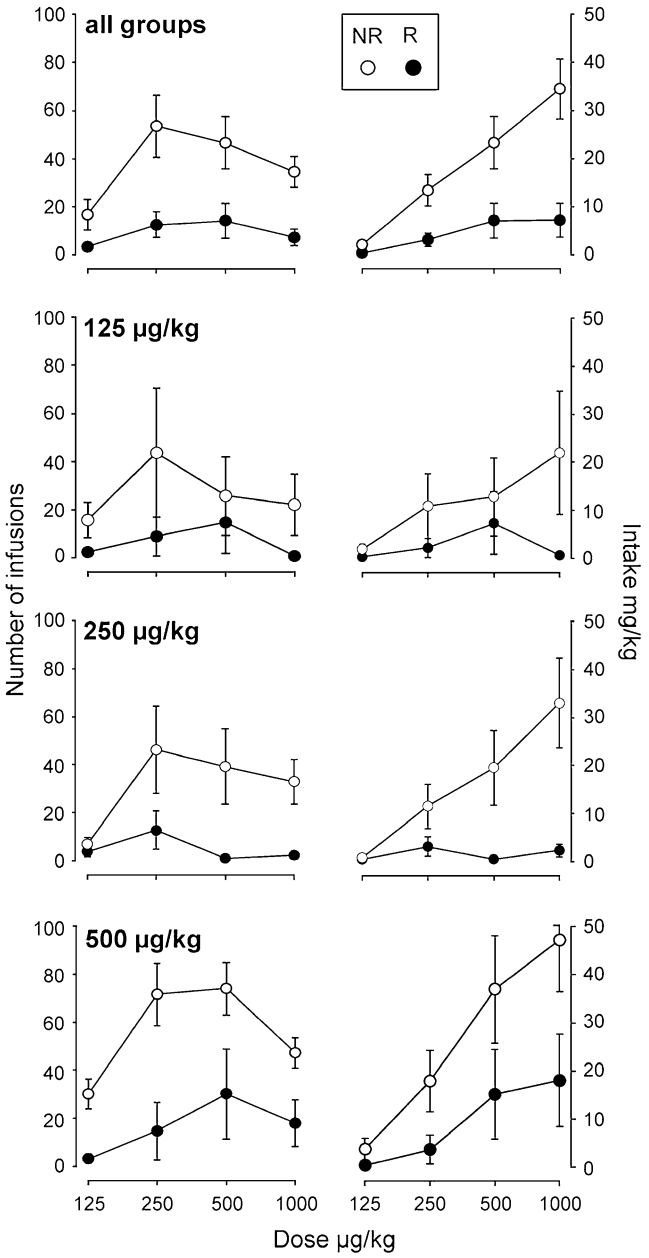

Fig. 4 Within-subject dose effect curve of ketamine self-administration (sessions 12–14). Each *symbol* indicates the mean number (±SEM) of infusions or the mean intake (±SEM) of ketamine (*left* and *right panels*, respectively) on a FR5 schedule of reinforcement

Discussion

The intravenous self-administration (SA) of ketamine in the rat has been previously described by others (Collins et al. 1984; Collins and Woods 2007). We now report that the setting of drug taking exerts a powerful influence on the propensity to acquire ketamine SA. Ketamine intake was much greater in rats that were transported to the SA chambers only for the test sessions (non-resident rats) than in rats housed in the SA chambers (resident rats).

Ketamine was synthesized in 1962 and developed as a "dissociative" anesthetic less toxic than phencyclidine, but its misuse was noted as early as 1971 (Jansen 2000) and has been reported on the rise over the past 15 years (Wu et al. 2006; Wolff and Winstock 2006). Ketamine can be taken through various routes of self-administration: intranasal, oral, inhalatory, intravenous, and intramuscular, and is frequently used to lace other street drugs. The population of ketamine users appears to be relatively small relative to that of other addictive drugs and yet this drug is very popular in certain contexts (Wolff and Winstock 2006; Degenhardt and Dunn 2008). Indeed, it has been reported that ketamine abuse is limited almost exclusively to individuals participating to music and dance events at nightclubs or rave parties, indicating a major role of context in modulating the reinforcing effect of this drug (Curran and Morgan 2000; Joe Laidler 2005; Degenhardt and Dunn 2008). Thus, the aim of the present study was to investigate at a pre-clinical level the role of setting for ketamine SA using an animal model developed in our laboratory (Caprioli et al. 2007a).

We have previously reported that amphetamine, cocaine, and heroin SA in the rat are influenced by the setting in which testing takes place. In particular, we have shown that environmental influences can alter in opposite directions the SA of psychostimulant vs opioid drugs. Indeed, it was

found that amphetamine and cocaine SA is greater in non-resident rats relative to resident rats, whereas heroin SA is greater in resident than in non-resident rats (Caprioli et al. 2007b, 2008). The neural substrates for these differences are still not known but an in situ hybridization study conducted using very low doses (self-administration doses) of heroin and cocaine indicated that these two drugs produce very different patterns of Fos mRNA expression in the posterior caudate of the rat brain as a function of context (Celentano et al. 2009).

These earlier findings were quite surprising because the dominant trend, at present, is to emphasize the role of shared substrates in the reward effects of addictive drugs. In particular, there is widespread consensus that the meso-corticolimbic dopaminergic system plays a pivotal role in drug reward (Nestler 2005). Nevertheless, it is well known each addictive drug is characterized by a unique pharmacokinetic and pharmacodynamic profile and it appears reasonable to assume that such unique profiles are the reason drugs can be distinguished from one another. Furthermore, there is evidence that even the dopaminergic system is differentially implicated in the reinforcing effects of psychostimulant vs opioid drugs (Ettenberg et al. 1982; Pettit et al. 1984; Dworkin and Smith 1988; Stinus et al. 1992; Gerrits and Van Ree 1996).

We have previously hypothesized that environmental influences on the reinforcing effects of drugs result from the evaluation of other drug effects in relation to the surrounding stimuli (Caprioli et al. 2009). Each addictive drug produces a distinctive constellation of desired and undesired effects, which may or may not partly overlap with that of other drugs. Some of these effects may be largely "indifferent" to environmental context whereas other effects would be more appropriate (or less inappropriate) to certain settings. The activating, performance-enhancing effects of cocaine and amphetamine, for example, would be experienced as more suitable to an exciting, relatively novel environment than to a home environment, as in the case of non-resident vs resident rats. In contrast, the sedative, inward-looking effects of heroin would be experienced as more appropriate to a safe, non-challenging, home environment. That is, the setting might affect drug choice by providing an ecological backdrop against which drug effects would be rated as more or less adaptive. Remarkably, the findings from a translational study conducted in human addicts coincided very closely with the results obtained in the rat (Caprioli et al. 2009). Most intravenous heroin and cocaine co-abusers reported in fact using heroin exclusively or mainly at home, and cocaine exclusively or mainly outside the home.

The reason for predicting that ketamine SA would be facilitated in non-resident relative to non-residents rats was threefold. The first two reasons concern the similitude between some of the effects of ketamine and those of psychostimulant drugs. Undoubtedly, the effects of ketamine are particularly complex, also in relation to the dose, and include, in addition to "dissociative" anesthesia, tachycardia, increased blood pressure, ataxia, hyperexcitability, agitation, acute psychotic episodes, unpleasant vivid dreams and hallucinations, and impaired cognitive function. However, at the doses used for recreational purposes, some of—but by no means not all—the physiological, behavioral and subjective effects produced by ketamine are similar to those produced by psychostimulant drugs (e.g., tachycardia, increased blood pressure, hyperexcitability, and agitation). Thus, it was reasonable to assume that they would be experienced as more appropriate to (or less aversive in) a non home vs a home environment as previously reported for cocaine and amphetamine (Caprioli et al. 2007a,b; 2008). More difficult is to speculate on how the setting may affect the evaluation of other effects of ketamine, such hallucinations and ataxia.

Also at a neurochemical level, some of the effects of ketamine are similar to those of amphetamine and cocaine, which are indirect dopamine agonists. In addition to its ability to block, in a non-competitive manner, NMDA receptors (Anis et al. 1983; Mendelson et al. 1984), ketamine has been reported in fact to increase dopamine efflux and block dopamine uptake in the nucleus accumbens (Hancock and Stamford 1999), and to possess partial agonist activity at dopamine D2 receptors (Kapur and Seeman 2002). Thus, both ketamine and psychostimulant drugs can activate dopaminergic transmission, albeit through different mechanisms of action.

Of course, the third and most important reason we predicted greater ketamine SA in non-resident relative to resident rats is that, as mentioned already, ketamine abuse in humans is exquisitely dependent on environmental conditions and in particular it appears to be limited to non-domestic settings (Curran and Morgan 2000; Joe Laidler 2005; Degenhardt and Dunn 2008).

A final issue deserves to be discussed here. Previous studies have shown that the magnitude of psychomotor sensitization induced by repeated administrations of amphetamine (Badiani et al. 1995a, 1997), cocaine (Badiani et al. 1995b; Hope et al. 2006), morphine (Badiani et al. 2000; Paolone et al. 2003), heroin (Paolone et al. 2007), and ketamine (Trujillo et al. 2007) is greater in a test environment different from the home cage (as our non-resident rats) than in rats treated and tested in their home cage (as our resident rats). The interest in psychomotor sensitization largely rests on the hypothesis that the underlying neuroadaptations are somewhat similar to those responsible for the development of drug addiction (Robinson and Berridge 1993). Thus, it is remarkable that environmental context appears to modulate in the same direction both sensitization and the reward effects of amphetamine, cocaine,

and ketamine. Also remarkable, however, is the dissociation observed between the psychomotor and reinforcing effects of heroin (Caprioli et al. 2008), further reinforcing the notion that heroin reward presents distinct features relative to psychostimulant drugs and ketamine.

In conclusion, the present findings confirm at a preclinical level the importance of setting for ketamine SA and further validate our animal model of drug-environment interaction. Further studies are necessary to investigate the neurobiological basis of this phenomenon.

References

Anis NA, Berry SC, Burton NR, Lodge D (1983) The dissociative anesthetics ketamine and phencyclidine, selectively reduce excitation of central mammalian neurons by N-methyl-aspartate. Br J Pharmacol 79:565–575

Badiani A, Anagnostaras SG, Robinson TE (1995a) The development of sensitization to the psychomotor stimulant effects of amphetamine is enhanced in a novel environment. Psychopharmacol Berl 117:443–4452

Badiani A, Browman KE, Robinson TE (1995b) Influence of novel versus home environments on sensitization to the psychomotor stimulant effects of cocaine and amphetamine. Brain Res 674:291–298

Badiani A, Camp DM, Robinson TE (1997) Enduring enhancement of amphetamine sensitization by drug-associated environmental stimuli. J Pharmacol Exp Ther 282:787–794

Badiani A, Oates MM, Robinson TE (2000) Modulation of morphine sensitization in the rat by contextual stimuli. Psychopharmacol Berl 151:273–282

Caprioli D, Paolone G, Celentano M, Testa A, Nencini P, Badiani A (2007a) Environmental modulation of cocaine self-administration in the rat. Psychopharmacol Berl 192:397–406

Caprioli D, Celentano M, Paolone G, Badiani A (2007b) Modeling the role of environment in addiction. Prog Neuropsychopharmacol Biol Psychiatry 31:1639–1653

Caprioli D, Celentano M, Paolone G, Lucantonio F, Bari A, Nencini P, Badiani A (2008) Opposite environmental regulation of heroin and amphetamine self-administration in the rat. Psychopharmacol Berl 198:395–404

Caprioli D, Celentano M, Dubla A, Lucantonio F, Nencini P, Badiani A (2009) Ambience and drug choice: cocaine- and heroin-taking as a function of environmental context in humans and rats. Biol Psychiatry 65:893–899

Celentano M, Caprioli D, Dipasquale P, Cardillo V, Nencini P, Gaetani S, Badiani A (2009) Drug context differently regulates cocaine versus heroin self-administration and cocaine- versus heroin-induced Fos mRNA expression in the rat. Psychopharmacol Berl 204:349–360

Collins RJ, Weeks JR, Cooper MM, Good PI, Russel RR (1984) Prediction of abuse liability of drugs using IV self-administration by rats. Psychopharmacol Berl 82:6–13

Collins GT, Woods JH (2007) Drug and reinforcement history as determinants of response-maintaining effects quinpirole in the rat. J Pharmacol Exp Ther 323:599–605

Curran HV, Morgan C (2000) Cognitive, dissociative and psychotogenic effects of ketamine in recreational users on the night of drug use and 3 days later. Addiction 95:575–590

Degenhardt L, Dunn M (2008) The epidemiology of GHB and ketamine use in an Australian household survey. Int J Drug Policy 19:311–316

Dworkin S, Smith J (1988) Molecular mechanisms of drug reinforcement—current status. NIDA Res Monogr 90:266–274

Ettenberg A, Pettit HO, Bloom FE, Koob GF (1982) Heroin and cocaine intravenous self-administration in rats: mediation by separate neural systems. Psychopharmacol Berl 78:204–209

Gerrits MA, Van Ree JM (1996) Effect of nucleus accumbens dopamine depletion on motivational aspects involved in initiation of cocaine and heroin self-administration in rats. Brain Res 713:114–124

Hancock PJ, Stamford JA (1999) Stereospecific effects of ketamine on dopamine efflux and uptake in the rat nucleus accumbens. Br J Anaesth 82:603–608

Hope BT, Simmons DE, Mitchell TB, Kreuter JD, Mattson BJ (2006) Cocaine-induced locomotor activity and Fos expression in nucleus accumbens are sensitized for 6 months after repeated cocaine administration outside the home cage. Eur J Neurosci 24:867–875

Jansen KLR (2000) A review of the nonmedical use of ketamine: use, users and consequences. J Psychoactive Drugs 32:419–433

Joe Laidler KA (2005) The rise of club drugs in a heroin society: the case of Hong Kong. Subst Use Misuse 40:1257–1278

Kapur S, Seeman P (2002) NMDA receptor antagonists ketamine and PCP have direct effects on the dopamine D(2) and serotonin 5-HT(2)receptors-implications for models of schizophrenia. Mol Psychiatry 7:837–844

Mendelson LG, Kerchner GA, Kalra V, Zimmerman DM, Leander JD (1984) Phencyclidine receptors in rat brain cortex. Biochem Pharmacol 33:3529–3535

Nestler EJ (2005) Is there a common molecular pathway for addiction? Nat Neurosci 8:1445–1449

Paolone G, Burdino R, Badiani A (2003) Dissociation in the modulatory effects of environmental novelty on the locomotor, analgesic, and eating response to acute and repeated morphine in the rat. Psychopharmacol Berl 166:146–155

Paolone G, Conversi D, Caprioli D, Bianco PD, Nencini P, Cabib S, Badiani A (2007) Modulatory effect of environmental context and drug history on heroin-induced psychomotor activity and fos protein expression in the rat brain. Neuropsychopharmacology 32:2611–2623

Pettit HO, Ettenberg A, Bloom FE, Koob GF (1984) Destruction of dopamine in the nucleus accumbens selectively attenuates cocaine but not heroin self-administration in rats. Psychopharmacol Berl 84:167–173

Robinson TE, Berridge KC (1993) The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res Brain Res Rev 18:247–291

Stinus L, Cador M, Le Moal M (1992) Interaction between endogenous opioids and dopamine within the nucleus accumbens. Ann NY Acad Sci 654:254–273

Trujillo KA, Zamora JJ, Warmoth KP (2007) Increased response to ketamine following treatment at long intervals: implications for intermittent use. Biol Psychiatry 63:178–183

Wu LT, Schlenger WE, Galvin DM (2006) Concurrent use of methamphetamine, MDMA, LSD, ketamine, GHB, and flunitrazepam among American Youths. Drug Alcohol Depend 84:102–113

Wolff K, Winstock AR (2006) Ketamine: from medicine to misuse. CNS Drugs 20:199–218