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Maria Teresa De Luca, Maria Meringolo, Primavera Alessandra Spagnolo and Aldo Badiani*

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Abstract: Drug abuse is often seen as a unitary phenomenon, partly as a result of the discovery over the past three decades of shared mechanisms of action for addictive substances. Yet the pattern of drug taking is often very different from drug to drug. This is particularly evident in the case of 'club drugs', such as ketamine. Although the number of ketamine abusers is relatively small in the general population, it is quite substantial in some settings. In particular, ketamine abuse is almost exclusively limited to clubs and large music parties, which suggests a major role of context in modulating the reward effects of this drug. This review focuses on recent preclinical and clinical findings, including previously unpublished data, that provide evidence that, even under controlled conditions, ketamine reward is a function of the setting of drug taking.

Keywords: cocaine; context; drug abuse; drug addiction; environment; hallucinogens; heroin; ketamine; opiates; psychostimulants; setting.

***Corresponding author: Aldo Badiani,** Department of Physiology and Pharmacology, Sapienza University of Rome, I-00185 Rome, Italy, e-mail: aldo.badiani@uniroma1.it
Maria Teresa De Luca: Department of Physiology and Pharmacology, Sapienza University of Rome, I-00185 Rome, Italy
Maria Meringolo: Department of Physiology and Pharmacology, Sapienza University of Rome, I-00185 Rome, Italy
Primavera Alessandra Spagnolo: Department of Physiology and Pharmacology, Sapienza University of Rome, I-00185 Rome, Italy
Aldo Badiani: Drug Addiction and Clinical Pharmacolgy Unit, University Hospital Umberto I, Sapienza University of Rome, 5 Piazzale Aldo Moro, I-00185 Rome, Italy

Introduction

Ketamine (ketamine chlorhydrate; CI-581) was synthesized by Calvin Stevens in 1962 at the Parke-Davis Laboratories in Michigan. The new drug was chemically related to phencyclidine (PCP) but presented clear advantages in terms of toxicity relative to the parent drug (Domino et al., 1965). Recovery (the 'emergence' period) from PCP-induced anesthesia is, in fact, associated with unwanted side effects, including confusion, unpleasant dreams and hallucinations (Siegel, 1978). Although ketamine also produces an emergence syndrome in 15%–40% of subjects (Dillon et al., 2001), its shorter half-life makes it more acceptable than PCP. Because of its relatively favorable safety profile, ketamine rapidly became an anesthetic of choice for the American army during the Vietnam War. The dissociative effects of ketamine (that is, its ability to induce a lack of responsive awareness to the environment) were particularly useful in the battlefield. Today, ketamine is still widely used as an anesthetic in developing countries and in remote rural areas of developed countries, such as Australia, because of the minimal equipment requirements for its administration. In addition, ketamine remains the most widely used anesthetic in veterinary medicine.

Ketamine's role in pain management goes beyond its use as a general anesthetic. Ketamine also has analgesic properties, preventing pain 'wind-up' [that is, the sensitization of neurons in the posterior horns of the spinal cord to pain stimuli (Sunder et al., 2008; Morgan and Curran, 2011)], and at low doses (0.1–0.5 mg/kg/h) produces a local anesthetic effect that is particularly useful in neuropathic pain (Correll et al., 2004; Lynch et al., 2005; Morgan and Curran, 2011). Ketamine has also been used in intensive care for the management of prolonged epileptic seizures (Fujikawa, 1995). Other potential medical uses of ketamine are currently under investigation. In particular, ketamine is being tested for the treatment of antidepressant-resistant mood disorders and for heroin and alcohol addiction (Krupitsky and Grinenko, 1997; Krystal, 2007; Aroni et al., 2009; Li et al., 2010; Vollenweider and Kometer, 2010).

Another interesting aspect of the pharmacology of ketamine concerns its psychotomimetic effects. Indeed, some effects of ketamine resemble the symptoms of acute psychosis (Adler et al., 1999). This has triggered research aimed at increasing our understanding of schizophrenia and at developing new therapies (Adler et al., 1999; Carpenter, 1999). The ketamine 'model' of schizophrenia is still the pharmacological model with the greatest face validity (Morgan and Curran, 2011).

The present review is not concerned with the medical uses of ketamine, nor with the ketamine model of psychosis, but centers exclusively on the recreational misuse of

ketamine. Ketamine is very popular with some people for its ability to produce hallucinations and an internal state similar to a trance. Indeed, ketamine is taken mainly in club settings, which indicates a major role of context in modulating the reward effects of this drug (Curran and Morgan, 2000; Joe Laidler, 2005; Degenhardt and Dunn, 2008). Thus, the review will focus on the role of context in ketamine abuse and, in particular, on recent experimental work conducted in rodents and humans.

Mechanisms of action of ketamine

Ketamine, like PCP, binds the N-methyl-D-aspartate (NMDA)-receptor complex at a site located within the channel (PCP-binding site). The excitatory amino acids glutamate, aspartate, and glycine are the endogenous agonists at the NMDA receptor. Activation of NMDA receptors results in the opening of the channel with increased transmembrane flux of Na^+, K^+ and Ca^{++}, and the depolarization of the neuron. Ketamine and PCP act as non-competitive NMDA receptor antagonists at the NMDA receptor.

Commercially available ketamine is a racemic mixture of two enantiomers. The S-enantiomer is the more potent of the two, with an anesthetic potency approximately three to four times that of R-ketamine. This correlates to the higher binding affinity for the PCP-site of the NMDA receptor. The psychotropic effects of ketamine are mainly caused by the S-enantiomer, although sub-anesthetic doses of R-ketamine have been shown to induce a state of relaxation (Engelhardt, 1997; Vollenweider et al., 2000).

The principal metabolite of ketamine, nor-ketamine, is pharmacologically active. Its binding affinity to the NMDA receptor and its anesthetic properties are approximately one-third of the parent compound, contributing significantly to the analgesic effect of ketamine (Shimoyama et al., 1999). The plasma levels at which ketamine analgesia is achieved are 0.15 μg/ml following intramuscular administration and 0.04 μg/ml after oral administration. This difference may be explained by the greater relative contribution of nor-ketamine after oral relative to intramuscular administration.

The anesthetic and analgesic effects of ketamine and PCP are not surprising given the role of NMDA receptors in the transmission of sensory inputs at the spinal, thalamic, limbic and cortical levels. Ketamine interferes not only with the perception of pain per se, but also with the emotional response to pain and with the formation of pain-related memories (Green and Johnson, 1990; Bergman, 1999; Sprenger et al., 2006). The analgesic effects of ketamine may depend, in part, on its agonist properties at mu-opioid receptors located at the spinal and supraspinal level (Fink and Ngai, 1982; Crisp et al., 1991; Sarton et al., 2001). Ketamine was also found to potentiate the activation of mu-opioid receptors by opioid agonists (Gupta et al., 2011). Furthermore, ketamine has been shown to prevent the development of morphine tolerance (Gonzalez et al., 1997) and suppress morphine withdrawal syndrome in experimental settings, probably by acting at the level of the nucleus accumbens (Ji et al., 2004).

Other effects of ketamine may be due to its actions on the catecholaminergic systems, notably on dopamine (DA) transmission (White and Ryan, 1996; Smith et al., 1998; Vollenweider et al., 2000). It has been shown that ketamine stereo-specifically increases DA efflux in the nucleus accumbens and in the prefrontal cortex by mobilizing the DA storage pool to releasable sites (Hancock and Stamford, 1999). In addition, ketamine has been shown to block DA reuptake (Hancock and Stamford, 1999) and activate D2 receptors (Kapur and Seeman, 2002). These dopaminergic effects may be implicated in the euphorigenic, addictive and psychotomimetic properties of ketamine. The initial ketamine-induced DA overflow in the prefrontal cortex undergoes tolerance after repeated administrations, whereas the increase in extracellular 5-hydroxyindole acetic acid (a serotonin metabolite) levels undergoes sensitization. This suggests that the balance between dopamine and serotonin neurotransmission in the prefrontal cortex may change after repeated exposure to ketamine (Lindefors et al., 1997). Ketamine also acts as an agonist at α- and β-adrenergic receptors (Bevan et al., 1997). Finally, ketamine has been shown to act as an antagonist at central muscarinic receptors and as an agonist at σ-receptors (Anis et al., 1983; Izquierdo et al., 1995; Bergman, 1999).

The psychotropic effects of ketamine can be observed in the presence of plasma concentrations ranging from 50 to 300 ng/ml and with regional brain concentrations higher than 500 ng/ml (Hartvig et al., 1995; Bowdle et al., 1998; Oranje et al., 2000).

Ketamine abuse

The non-medical use of ketamine dates from the late 1960s, when the drug began spreading from the Parke-Davis Laboratories in Michigan to other states, particularly Florida, where it was sold as a hallucinogen with names such as 'mean green' and 'rockmesc' (i.e., 'rock mescaline') (Jansen, 2004). Ketamine use remained relatively

rare in Europe until the 1990s, when it appeared on the 'rave' scene as an adulterant to ecstasy (3,4-methylenedioxy-*N*-methylamphetamine; MDMA) tablets (Dalgarno and Shewan, 1996). Other street names of ketamine are 'Special K', 'Vitamin K', 'K', 'Kit-kat', 'Keets', 'super acid', 'cut valium', and 'jet'.

Users report that ketamine is easier to take than other hallucinogenic drugs such as LSD and that its hallucinogenic effects are more manageable, owing to a predictable dose-response curve of effects and a relatively short half-life (Dillon et al., 2003; Wolff and Winstock, 2006).

Ketamine is highly lipophilic and can be taken through various routes of administration: intranasal (snorting), intramuscular, oral, intravenous, subcutaneous and inhalatory (smoking). Snorting represents the most popular route of administration. Dosing devices for snorting ketamine are called 'bullets' or 'bumpers' (Chakraborty et al., 2010). Ketamine is often snorted in combination with other drugs ('trail mix'), such as methamphetamine, cocaine (the so-called 'Calvin Klein'), sildenafil citrate or heroin (Tellier, 2002). Other popular drug combinations are taken orally (e.g., ketamine and MDMA) or via smoking (ketamine and cannabis).

At low doses, ketamine induces distortion of time and place, hallucinations and bizarre dissociative effects. According to many users, the most appealing effects of ketamine are represented by 'melting into the surroundings', 'visual hallucinations', 'out-of body experiences', and 'giggliness' (Stewart, 2001). At higher doses, ketamine induces more severe dissociation, commonly referred to as 'K-hole', with the users experiencing intense detachment to the point that their perception appears to be completely divorced from their previous reality. Some users enjoy the experience of a K-hole and describe themselves as 'psychonauts' (see below), whereas others strongly dislike the resulting decrease in sociability (Dillon et al., 2001).

According to the 2012 Ketamine Critical Review Report by the Expert Committee on Drug Dependence of the World Health Organization (WHO), in developed countries, street ketamine comes from two main supply sources: hospitals and veterinary clinics on the one hand, and illegal import from developing countries on the other. In the past, hospitals and veterinary clinics represented the main source of ketamine. This sort of supply is the most appreciated by consumers, as quality control is guaranteed by the pharmaceutical industry. Increasing regulatory control has made it more and more difficult, but not impossible, to obtain medical ketamine. Presently, street ketamine is mostly obtained from countries where it is still easily available, mainly China and India (Jansen, 2004).

Geographical distribution of ketamine abuse

As indicated by the 2010 United Nations World Drug Report, ketamine abuse is a global phenomenon with large geographical variation. In Hong Kong, for example, ketamine is thought to be the single most abused illicit drug, coming mostly from mainland China. However, although China produces massive amounts of ketamine, reliable estimates for the prevalence of ketamine abuse are not available. As of today, five Chinese factories are officially licensed to produce ketamine, but there are reports of illicit production on an industrial scale. In 2009, Chinese authorities reported the seizure of two illicit laboratories producing 8.5 million tons of the immediate precursor of ketamine.

Despite the efforts of several research groups, little is known of the epidemiology of ketamine abuse in other countries (WHO Expert Committee on Drug Dependence, 2012). Topp et al. (2004) describe the Australian Illicit Drug Reporting System (IDRS) and the feasibility of monitoring market trends for 'party drugs'. The trial demonstrated that the system can successfully monitor the market for widely used drugs, such as ecstasy, whereas it is much less sensitive in monitoring the markets for drugs that are used by small proportions of the total population, such as ketamine and other 'club drugs'.

In the USA, according to an official 2009 NIDA publication, an estimated 1%–2% of 10th–12th graders reported having used ketamine (Johnston et al., 2009). More uncertain are the numbers for Europe. Reports of widespread recreational use of ketamine in the UK began to appear in the literature from the early 1990s (Jansen, 1993; Dalgarno and Shewan, 1996). Estimates suggest an increase in the number of ketamine users from approximately 85,000 in 2006/2007 to approximately 113,000 in 2008/2009 (Hoare, 2009). Additional evidence of the growing recreational use of ketamine in the UK has been provided by others (Measham et al., 2001; Moore, 2004; Copeland and Dillon, 2005; Moore and Measham, 2008).

France is another country where ketamine use appears to be significant. As detailed in the 2010 France National Report to the European Monitoring Centre for Drugs and Drug Dependence (EMCDDA 2010c), the Centres d'Accueil et d'Accompagnement à la Réduction des Risques pour Usagers de Drogues (CAARUD) found that among the most striking changes in drug use and method of use there in the years 2008–2009 was the spreading of ketamine misuse outside the alternative party scene (see below). More than 7% of addicts

referred to the CAARUDs reported recent use of ketamine (approx. 5% reported daily use). In the general population of 17 year-olds, ketamine use was estimated at 0.6% (0.8% in males and 0.4% females). Furthermore, according to the same report, although in previous years the first encounter with ketamine was almost a chance event, this drug is now actively desired and sought out by new users. That is, ketamine is in the process of becoming a 'first experimentation' substance for some individuals.

An increase in the recreational use of ketamine has been observed in other European countries as well (EMCDDA, 2011). Eight out of the 29 EMCDDA participating countries provided some information about ketamine use (in addition to the UK and France: Czech Republic, Denmark, Hungary, Ireland, Italy, and the Netherlands). The 2010 Czech Republic National Report to the EMCDDA (EMCDDA, 2010b), for example, included data from the 2009 Safer Party Tour project (which provided preventive and harm reduction services at 14 summer festivals) indicating that the lifetime use of ketamine among Safer Party affiliates was 10.8%. Similar data were contained in the 2010 The Netherlands National Report to the EMCDDA (EMCDDA, 2010d), which indicated an 8.5% prevalence of ketamine use among participants in large scale parties (raves) and 4.1% among visitors of clubs and discotheques.

However, the quality of the reports from the different participating countries was not homogeneous, and it is not easy to understand to what extent the lack of data in a report reflects little or negligible ketamine abuse or simply a lack of reliable information. For example, the 2010 Austria National Report to the EMCDDA (EMCDDA, 2010a) makes no mention of ketamine, but the 2007 report (EMCDDA, 2007) details the findings of a survey carried out on the spot at free techno and Goa-like events, according to which 23% of all participants used ketamine (Baumgartner, 2007). This was also the case for the reports of other countries.

Demographics of ketamine abuse

The large majority of ketamine users have a significant history of polydrug use, often confined to parties, more rarely as part of daily use activity. Generally, the first use of ketamine occurs in a group at a rave. Indeed, all available evidence shows that ketamine abuse is, at least initially, framed within the context of rave parties. Raves are parties with loud, electronic 'techno-rock' music, laser light shows and all-night dancing held in clandestine locations, including warehouses, nightclubs and farm fields (Weir, 2000). They first became popular in the UK and the USA in the late 1980s and have since spread to other countries.

Many of the early ketamine users were jobless and without a fixed residence, their lifestyles being focused mainly on drug consumption and on the organization of raves. More recently, ketamine use has moved beyond the context of raves and has become popular in youth clubs whose clients have been in contact with the rave culture. In parallel with the spread of ketamine to mainstream discos and clubs, the social profile of users has become less marginal.

Reynaud-Maurupt et al. (2007a) argue that, among ketamine users, four 'affinity groups' can be identified on the basis of distinct socio-demographic profiles and different levels of consumption: 'alternative', 'urban', 'clubbing' and 'selected'.

The 'alternative' group is composed by counterculture enthusiasts with a hedonistic tinge. The setting of ketamine taking is represented by rave and free parties. It has been argued that this group can be further subdivided into Ravers and Travellers. Ravers come from the rave and 'teknival' culture. They consume ketamine by sniffing and are socially functional. The Travellers' lifestyle focuses on drug consumption and parties. They live in unstable conditions and frequently experience problems derived from drug consumption. Travellers often inject ketamine.

The 'urban party' group is music-oriented, and its habitat is represented by live music bars. Individuals in this group are well integrated at a social level and are characterized first and foremost by their fondness for music. This group includes the highest percentage of students.

The 'clubbing' group is composed by hedonists who devote a substantial portion of their budget to partying and buying clothes. Their habitat is represented by clubs playing electronic music. The 'gay friendly' establishment belongs to this particular affinity group.

The 'selected' group is composed by individuals who attend invitation-only or sponsored-entry bars or clubs requiring 'smart dress' attires. The standards of living of these users are quite high, and there is very little overlap with the other groups. The selected group frequents locations usually accessed through coopting and cultivates a chic and hip image.

Finally, a particular population of ketamine users is represented by the 'psychonauts'. The term psychonautics is of recent coinage and has entered scholarly literature even more recently (e.g., Ott, 2001). Psychonauts may consume ketamine and other psychedelic drugs

('entheogens'), to induce an altered state of consciousness, thereby facilitating the 'exploration' of the psyche. As their main goal is introspection, psychonauts use ketamine in quiet places and usually by injection. Presently, psychonauts represent a minority of ketamine users (Newcombe, 2008).

The setting of ketamine use

Environment plays an important role in modulating individual responsiveness to addictive drugs (Caprioli et al., 2007a; Badiani et al., 2011). For example, adverse life experiences (e.g., sexual abuse/harassment, combat-stress, occupational stress and other forms of social and physical stress) can facilitate the initiation and the development of drug abuse and then of drug addiction and, by acting acutely, can precipitate drug seeking after a period of abstinence (Aro, 1981; Triffleman et al., 1995; Richman et al., 1996; Brady et al., 2001; Clark et al., 2001; Price et al., 2004; Ompad et al., 2005; Brown et al., 2006; Reed et al., 2006). Another way the environment can affect drug taking is represented by drug-associated cues that can trigger drug seeking even after prolonged abstinence (Childress et al., 1984, 1986).

Also in the case of ketamine abuse, context appears to play a major role. As discussed above, ketamine abuse is, in fact, prevalent among individuals participating in music and dance events at nightclubs or rave parties (Curran and Morgan, 2000; Joe Laidler, 2005; Degenhardt and Dunn, 2008). This anecdotal evidence has recently received support from animal and human studies, which will be reviewed below, along with unpublished data that will be presented here for the first time.

Setting of ketamine use: pre-clinical studies

Preclinical research concerning the role of context in drug addiction has focused mostly on the ability of environmental stimuli to act as stressors or as drug cues. However, context has been shown to affect drug taking in ways that are not easily attributable to stress or conditioning. For example, the presence of novel objects has been found to reduce the intake of amphetamine (Klebaur et al., 2001), and high temperatures can increase the intake of 3,4-methylenedioxymethamphetamine (Cornish et al., 2003). Even nonphysical, apparently negligible differences in the setting can powerfully alter drug-taking behavior, as indicated by a series of studies in which rats were trained to self-administer heroin or cocaine under two deceptively similar environmental conditions. Some rats were transferred to the self-administration chambers immediately before the experimental sessions (non-resident rats), a procedure commonly used in most self-administration studies. Other rats were kept in the self-administration chambers at all times (resident rats). Thus, the physical characteristics of the self-administration environment for resident vs. non-resident rats were virtually identical, all differences being purely a function of familiarity. As illustrated in the top panels of Figure 1, we found that psychostimulant drugs, such as cocaine and amphetamine, were self-administered more by non-resident rats than by resident rats, whereas the opposite occurred with heroin self-administration (Caprioli et al., 2007b, 2008; Celentano et al., 2009). The influence of setting on drug taking was particularly striking in experiments in which rats with double-lumen catheters were repeatedly given the opportunity to choose between two drugs within the same session (Caprioli et al., 2009). In fact, most non-resident rats chose cocaine over heroin, whereas resident rats tended to prefer heroin.

We have hypothesized that the setting may affect drug taking by providing an ecological backdrop against which drug effects are appraised as more or less 'adaptive' (Caprioli et al., 2009; Badiani et al., 2011). Briefly, we proposed that the sedative, inward-looking effects of heroin 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 (this hypothesis will be discussed in more detail at the end of this review). On the basis of this initial hypothesis, we speculated that drugs producing effects somewhat similar to those of psychostimulants or opiates would also interact with the environment in a similar manner. Indeed, we found that ethanol, which, at least at certain doses, depresses the central nervous system similar to opiates, was ingested in greater amounts by resident rats than by non-resident rats (Testa et al., 2011).

Most important, we also predicted that the intravenous self-administration of ketamine (first reported by Collins et al., 1984) would be greater in non-resident rats than in resident rats. 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, hyper-excitability, agitation, acute psychotic episodes, unpleasant vivid dreams, hallucinations and impaired cognitive function. However,

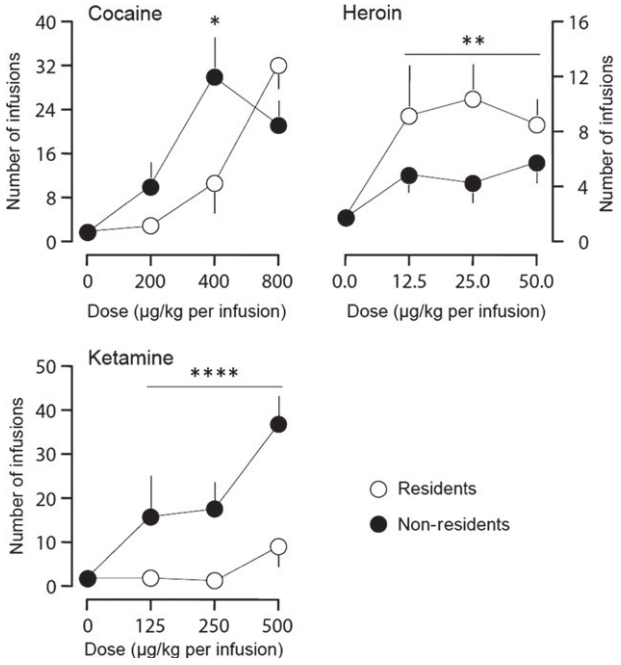

Figure 1 Drug taking as a function of setting in rats.
This figure is based on previously published data (Caprioli et al., 2007b for cocaine; Caprioli et al., 2008 for heroin; De Luca et al., 2011 for ketamine) and illustrates the mean (±SEM) number of infusions on the last day of the training phase (FR5 schedule of reinforcement) as a function of the setting. The data for each infusion dose were obtained in independent groups of rats (n=11–15 for cocaine; n=12–16 for heroin; n=6–10 for ketamine). Resident rats were housed in the self-administration chambers. Non-resident rats were transferred to these chambers only for the test sessions (3 h each). Asterisks indicate significant differences (*p<0.05; **p<0.01, ****p<0.0001) between resident and non-resident groups. For details of the statistical analyses, see the original publications.

at the doses used for recreational purposes, some, but by no means all, of the physiological, behavioral and subjective effects produced by ketamine are similar to those produced by psychostimulant drugs, e.g., tachycardia, increased blood pressure, hyper-excitability and agitation. Thus, it was reasonable to assume that these effects 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 to speculate on is how the setting affected the appraisal of other effects of ketamine, such as hallucinations and ataxia.)

There is a partial overlap between ketamine and psychostimulants also with regard to the mechanisms of action, as ketamine has been reported to increase dopamine efflux and reduce dopamine uptake in the nucleus accumbens (Hancock and Stamford, 1999). Finally, the fact that ketamine abuse in humans is associated with clubs or rave parties (Curran and Morgan, 2000; Joe Laidler, 2005; Degenhardt and Dunn, 2008) also leads us to predict greater preference for ketamine in non-resident than in resident rats.

Consistent with our hypothesis, we found that ketamine intake was much greater in non-resident rats than in resident rats (De Luca and Badiani, 2011). The bottom left-hand panel of Figure 1 illustrates the dose-response curve for ketamine self-administration. Non-resident rats acquired ketamine self-administration at all training doses, whereas resident rats self-administered only the highest dose of ketamine (500 µg/kg), but still four times less than non-resident rats (De Luca and Badiani, 2011).

The role of setting in ketamine (Parke-Davis, Detroit, MI, USA) self-administration is also indicated by the results of an experiment in which rats were given the opportunity to choose between ketamine and heroin (S.A.L.A.R.S., Como, Italy) within the same session. These findings are reported here for the first time. The experimental procedures were similar to those described by Caprioli et al. (2009). Briefly, 14 male Sprague-Dawley rats (Harlan, Italy), weighing 250–275 g at their arrival, were housed and tested in the same dedicated temperature and humidity-controlled rooms, with free access (except during the test sessions) to food and water under a 14-h dark/10-h light cycle (lights off at 7:00 am). After the surgery, the rats were housed individually. 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 the Italian Ministry of Health. Using standard surgical procedures, the rats received double-lumen catheters connected with cannulas secured to the rat's skull, as described by Caprioli et al. (2009). At the end of the experiments, all rats underwent a catheter patency test in which they received two i.v. boluses of 40 mg/kg of thiopental sodium (Pharmacia Italia, Milan, Italy), one in each catheter, with a 15-min interval between the two. No rat failed the test, that is, all rats became ataxic within 5 s after thiopental. The testing apparatus (ESATEL S.r.l., Rome, Italy), described in detail in previous papers (Caprioli et al., 2009), consisted of self-administration chambers placed within sound- and light-attenuating cubicles and equipped with two retractable levers, two light cues positioned above each lever and a counterbalanced arm holding a liquid swivel. Each lever was connected via an electronic interface to a syringe pump (Razel Scientific Instruments, St. Albans, VT, USA). Personal computers controlled the chambers, via Programmable Logic Controller (Allen Bradley, Milwaukee, WI, USA), using control software developed by Aries Sistemi S.r.l. (Rome, Italy).

During the training phase, the rats were assigned to one of two conditions: resident and non-resident. Resident rats were housed in the self-administration chambers, where they remained for the entire duration of the experiment. Non-resident rats (n=8) were housed in standard cages and were transferred to the self-administration chambers immediately before the start of each testing session.

Resident rats (n=6) were connected, through liquid swivels, to the infusion lines 3 h before the start of each session. During the 60 s preceding the start of each session, food and water were removed from the chambers, and the infusion pumps were activated so as to fill the catheters with the drug solution. Immediately before the start of each session, non-resident rats were transferred to the self-administration chambers, and their catheters were connected to the infusion lines. At the end of each session, food and water were given back to the resident rats and non-resident rats were returned to their home cages. The rats were trained for 10 consecutive daily 3-h sessions to self-administer ketamine (250 μg/kg/infusion). Ketamine was alternatively paired with one or the other of the two levers, according to a counterbalanced design. That is, for some rats, ketamine was paired with the left lever on sessions 1, 3, 5, 7 and 9, whereas pressing on the right lever had no programmed consequences; the opposite occurred on sessions 2, 4, 6, 8 and 10. For other rats, the sequence was inverted. After each infusion, the cue light was turned off, and the lever retracted. The cue light was turned on and the lever extended again after a time-out (TO) period. Both the fixed ratio (FR, i.e., number of consecutive lever presses required to obtain a single infusion) and the TO period progressively changed during training, to habituate the rats to obtain an infusion every 10 min. The FR increased from FR1 (sessions 1–2, with a 40-s TO, and sessions 3–4, with a 60-s TO), to FR2 (sessions 5–6, with a 2-min TO, and sessions 7–8, with a 3-min TO), and finally to FR5 (sessions 9–10, with a 5-min TO, and sessions 11–12, with a 10-min TO). The goal was to reach, by the end of the training phase, the same reinforcement schedule used during the subsequent choice phase.

During the choice sessions, some rats were given the opportunity to choose between ketamine and heroin, each paired with one of the two levers. Other rats instead received ketamine regardless of the chosen lever (that is, the 'choice' was between ketamine and ketamine). Both levers were available simultaneously at time 0 min and then again 10 min after each infusion. The doses of ketamine and heroin were progressively increased during 12 choice sessions (3-h each). During sessions 1–4, rats had a choice between 250 μg/kg ketamine and either 25 μg/kg heroin or 250 μg/kg ketamine. During sessions 5–8, rats had a choice between 500 μg/kg ketamine and either 50 μg/kg heroin or 500 μg/kg ketamine. During sessions 9–12, rats had a choice between 1000 μg/kg ketamine and either 100 μg/kg heroin or 1000 μg/kg ketamine. At the end of the experiments, all rats underwent a catheter patency test using thiopental, as described above.

The following is a synopsis of the environmental conditions of resident and non-resident rats: 1) the self-administration environment was physically identical for all rats, but for some animals this was also the home environment (resident group), whereas for other animals it represented a distinct non-home environment (non-resident group); 2) immediately before the start of each session, the resident rats were briefly handled to remove food and water from the chamber; 3) during testing, the self-administration chambers contained no food or water; 4) the distance traveled by the non-resident rats during the transfer to the self-administration chamber was about 1 m (that is, all animals were kept in the same dedicated testing room for the entire duration of the experiments, and therefore there was no transport from one room to another); and 5) all other husbandry routines were identical in the two groups.

In summary, the differences in setting between resident and non-resident rats were of a purely 'psychological' nature. Yet, these apparently negligible differences were capable of altering drug preferences in a substantial manner.

During training, resident rats took much less ketamine than non-resident rats (data not shown), in agreement with the findings by De Luca et al. (2011). Furthermore, when, during the choice phase, resident rats had access to ketamine on both levers, they took very little of it, regardless of the infusion dose, whereas non-resident rats worked for ketamine on both levers, in a dose-dependent manner (Figure 2). An analysis of variance (ANOVA) limited to ketamine intake indicated, in fact, a significant effect of setting [$F(1,13)=6.53$, $p=0.024$] and a significant setting × dose interaction [$F(2,26)=9.47$, $p<0.001$]. In contrast, when resident rats had the opportunity to choose between ketamine and heroin, they eagerly took heroin, but not ketamine, following a dose-dependent pattern. The ANOVA yielded a significant effect of drug [$F(1,2)=6.75$, $p=0.016$] and a drug × dose interaction [$F(2,4)=22.93$, $p=0.006$]. This indicates that the lower propensity of resident rats to self-administer ketamine was drug-specific and did not reflect a general inability to acquire drug-reinforced instrumental behavior. In contrast, non-resident rats that were given the choice between ketamine and heroin took, overall, about the same amount of the two drugs [$F(1,3)=0.42$,

p=0.56], although, at the two highest doses, non-resident took about 60% (K50 vs. H500) and 35% (K100 vs. H1000) more ketamine than heroin. We investigated here a very limited combination of drug doses. It is quite possible that at certain doses (e.g., 50 μg/kg of ketamine vs. and 1000 μg/kg of heroin). Non-resident rats would have expressed a more robust preference for ketamine over heroin. Notice, however, that the most remarkable aspect of the present results (as well as of those reported in our previous papers) does not lie with the drug preferences of resident rats per se or non-resident rats per se, but with the comparison between the two groups, as this comparison indicates that the reinforcing effect of a given dose of a given drug changes as a function of the 'psychological' setting in which the drug is taken.

Setting of ketamine use: clinical studies

The fact that certain settings were able to modulate in opposite directions cocaine (or amphetamine or ketamine) vs. heroin self-administration in rats (Caprioli et al., 2007b, 2008, 2009; Celentano et al., 2009) indicated an unforeseen dissociation in the reinforcing effects of different classes of addictive drugs, which is not compatible with unitary models of drug reward (for an in-depth discussion of this issue, see Badiani et al., 2011).

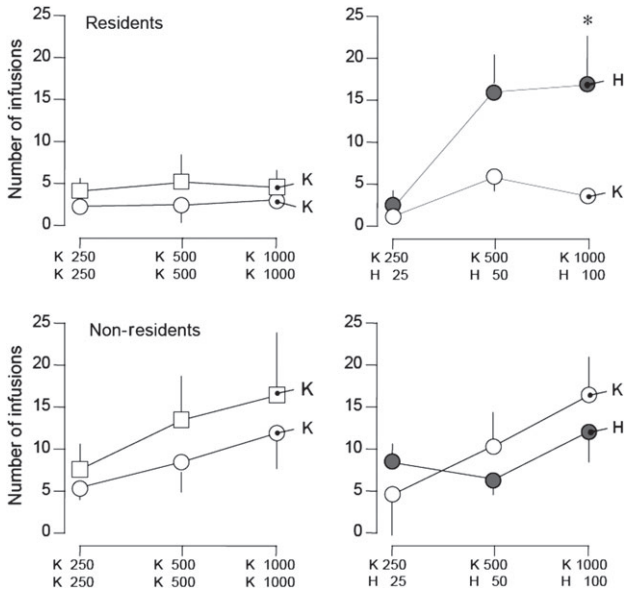

Figure 2 Drug preferences as a function of setting in rats. This figure illustrates the mean (±SEM) number of drug infusions in resident (n=6) vs. non-resident (n=8) rats with double-lumen catheters that were repeatedly given the choice between two drug rewards. For some rats, the choice was between identical doses of ketamine (left-hand panels). Other rats had a choice between ketamine and heroin. Asterisks indicate significant differences (*p<0.05) between heroin and ketamine. For details of the statistical analyses, see the text.

The heuristic relevance of these animal findings is indicated by the results of translational studies in which we investigated the setting of drug taking in human addicts (n=79) who co-abused heroin and cocaine (Caprioli et al., 2009). As illustrated in Figure 3, the majority of addicts reported using heroin always or mostly at home and cocaine always or mostly outside the home. Participants were cocaine and heroin addicts recruited among the out-patients of an addiction clinic (Villa Maraini, Rome, Italy) who: 1) met the DSM-IVR drug dependence criteria for cocaine and/or heroin; 2) reported using heroin and/or cocaine [either drug for the Retrospective Reports study, both drugs for the Momentary Ecological Assessment (EMA) study] at least once a week over the past 3 months; 3) did not meet the DSM-IVR criteria for schizophrenia or any other DSM-IV psychotic disorder, history of bipolar disorder or current major depressive disorder; 4) were not under treatment with antipsychotic medications; 5) did not have cognitive impairment severe enough to preclude informed consent or valid self-reporting; 6) did not have other medical conditions that would compromise participation in the study; and 7) had a fixed address. Approximately 74% of participants reported injecting heroin exclusively, or mostly, at home, whereas approximately 22% preferred to take it exclusively, or mostly, outside the home. The opposite was true for cocaine. A small number of subjects did not express a clear preference for home vs. non-home environments (these individuals were indicated as "50/50" in Figure 3). Virtually identical results were obtained when the analysis was limited to individuals who took both drugs either intravenously or intranasally, indicating that the choice of the setting was not driven by the route of drug taking. We have recently confirmed these results in a study using the EMA technique (Spagnolo et al., 2011).

We used a similar approach to investigate the setting of ketamine use in humans. Preliminary data from this study (n=19) are reported here. In agreement with the findings obtained in rodents, most ketamine users reported taking the drug outside the home rather than at home (Figure 3, right-hand panel). The specific non-home settings of ketamine use were: parties (100%), raves (40%), Goa-like parties (30%), friends' place (30%) and rave festivals (20%). (Notice that each subject could indicate more than one setting.) In the process of conducting this study, we became aware of two previous papers reporting similar

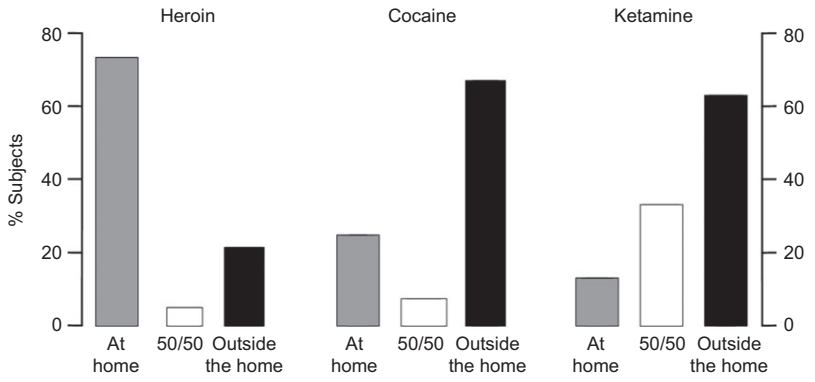

Figure 3 Setting preferences for heroin, cocaine and ketamine use in humans, as indicated by retrospective reports.
The data for cocaine and heroin use in addicts co-abusing the two substances (n=79) were published previously (Caprioli et al., 2009). The ketamine data (n=19) are reported here for the first time.

findings. Dillon et al. reported that home was the preferred setting of ketamine use in 16% of cases, vs. 47% at dance and rave parties, 26% at clubs, 10% at the homes of friends and 1% at pubs (Dillon et al., 2001, 2003). Reynaud-Maurupt et al. (2007b) also investigated the circumstances of ketamine use and found that the last dose was taken in private home settings in 35% of cases (notice that this survey did not distinguish between the homes of users and the homes of their friends) vs. non-home environments in 65% of cases (23% at free parties, 14% at techno festivals, 6% at squat parties, 5% at rave parties and 5% in clubs).

Conclusions

We have previously hypothesized that environment influences the reward effects of drugs as a result of the appraisal of drug effects in relation to the surrounding stimuli (Caprioli et al., 2009; Badiani et al., 2011). Each addictive drug produces a distinctive constellation of desired and undesired effects, which may or may not partly overlap with those of other drugs. Some of these effects may be largely indifferent to an environmental context, whereas other effects would be more appropriate (or less inappropriate) in 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. In contrast, the sedative, inward-looking effects of heroin would be experienced as more appropriate to a safe, non-challenging home environment. That is, we hypothesize that the setting might affect drug choice by providing an ecological backdrop against which drug effects are appraised as more or less 'adaptive'. It is important to emphasize that emotional appraisal does not necessarily entail the conscious evaluation of stimuli (see, for example, LeDoux, 1996, 2012). Thus, the fact that heroin is preferentially taken at home should not be seen as a mere expression of an intentional decision to take a 'downer' where you can 'slouch on the sofa'. It would be difficult to envisage such a mental process in the case of our resident rats, not only because attributing conscious planning to rats would be questionable at best. Indeed, resident rats did not have a choice between different settings but simply adapted their behavior to the context by taking less cocaine (or amphetamine or ketamine) and more heroin relative to non-resident rats.

As previously discussed, one of the reasons for predicting that the self-administration of ketamine, like that of cocaine and amphetamine, would be facilitated in non-resident rats relative to resident rats, was based on the existence of some similarities in the behavioral, physiological and neurochemical effects of ketamine and psychostimulant drugs. Of course, another major reason for predicting greater preference for ketamine in non-resident than in resident rats was the anecdotal evidence that ketamine abuse in humans is associated with clubs or rave parties (Curran and Morgan, 2000; Joe Laidler, 2005; Degenhardt and Dunn, 2008). Remarkably, the findings of human studies (in addition to the data presented here, see Dillon et al., 2001 and Reynaud-Maurupt et al., 2007a) coincided very closely with the results obtained in the rat. In our study, only a minority of users (about 10%) reported using ketamine exclusively, or mostly, at home. These users probably correspond to the 'psychonauts', who are known to titrate the dose to produce an internal state that is not compatible with social gatherings and requires instead quiet environments.

The clinical and pre-clinical findings reviewed here confirm the anecdotal evidence of a major role of setting

for ketamine use. In particular, the study conducted in rats under controlled conditions indicate that the physical environment may affect ketamine reward at a very fundamental level, independent, at least in part, of social interactions. Furthermore, these and other findings (see, for example, Badiani et al., 2011) challenge that notion that drug reward (and more in general reward *tout court*) represents a unified phenomenon, almost invariant of the specific psychopharmacological profile of the various drugs. Much can be learned about the neurobiological underpinning of drug reward by taking into consideration the emotional appraisal of the specific effects produced by each drug within the context of the surrounding environment.

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