Ketamine acts as an internal contextual stimulus that facilitates the retrieval of weak associations in conditioned taste aversion

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Ketamine (6 mg/kg), when injected intraperitoneally into Long-Evans rats during both the acquisition and the test phases, was found to facilitate the retrieval of a conditioned taste aversion (CTA) based on pairings of a flavor with lithium chloride (LiCl). This facilitation was not a monotonic function of LiCl dosage, since it was observed with only 15.90 mg/kg and not 7.95, 31.80, 63.60, or 127.20 mg/kg. In our conditions, 15.90 mg/kg of LiCl is a dosage that elicits a weak CTA. This result suggests that ketamine acts like a contextual cue, which facilitates the retrieval of weak but not of strong associations. This result is discussed in the framework of drug-induced state dependency, and compared with the effects of external contextual cues.

State-dependent learning—or more precisely, *state-dependent retrieval* (SDR)—refers to the fact that information learned in a given state can be recalled better or exclusively when a subject is tested in this state, but not when the subject is tested in a state different from that in which the information was acquired (Overton, 1978; Weingartner, 1978). A variety of states have been shown to elicit SDR, such as affective states (see, e.g., Bower, 1981), endogenous biorhythm-induced states (e.g., Evans, Gustafson, O'Connell, Orne, & Shor, 1966; Holloway, 1978), or drug-induced states (see Overton, 1982). Drug-induced SDR is still considered by some authors as a non-specific, degenerate phenomenon, closely dependent on the discriminative properties of the pharmacological agents (Overton, 1982; Järbe, 1986, 1987). This view was initially prompted by the observation that the doses of drugs at which state dependency had typically been observed were found to be intoxicating (Overton, 1966, 1982) or sublethal (Overton, 1972), and thus too high to be relevant to the characteristic behavioral actions of these agents. However, Colpaert (1986, 1990) and Jack-

son, Koek, and Colpaert (1992), testing benzodiazepines and NMDA antagonists, have recently demonstrated that drug-induced SDR constitutes a robust phenomenon with low doses of drugs that do not disrupt behavior. Consequently, Colpaert proposed that state dependency could constitute a rather general mechanism by which drugs act on memory processes (see also Colpaert, Nieмеgeers, & Janssen, 1976).

Among the various possible mechanisms that have been proposed for SDR, one is that a drug could constitute an internal contextual cue that modulates memory processes in the same way as do external contextual cues; that is, the SDR phenomenon could be seen as an instance of contextual learning. To date, this hypothesis has been supported mainly by the general finding that a shift of drugged state between the acquisition and the retrieval phases impairs performances, just as is observed with a shift of external context (for a review, see Overton, 1985; see also Bouton, Kenney, & Rosengard, 1990).

Additionally, in favor of the hypothesis that drug-induced internal cues act as a context, changes in exteroceptive context and in drug state have been found to interact to affect retrieval (see, e.g., Connelly, Connelly, & Epps, 1973; Connelly, Connelly, & Nevitt, 1977; Connelly, Connelly, & Phifer, 1975). For example, Duncan (1979) showed that the SDR effects of ethanol were insignificant if retrieval testing occurred in the same compartment as that in which the animals had been trained, but

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were obvious if the animals were tested in a different compartment. In Duncan's study, the change in external contextual cues apparently acted to unmask an SDR effect that was not expressed without a concurrent environmental contextual change.

External contextual cues have been repeatedly shown to control associations between stimuli, but only to the extent that the strength of an association is low enough to support modulation (e.g., Bonardi, Honey, & Hall, 1990; Lovibond, Preston, & Mackintosh, 1984). When the strength of the association increases, the modulation by external contextual cues tends to disappear. To date, whether this characteristic aspect of external contextual control applies to drugs remains to be tested. If a drug that induces SDR acts as a contextual cue, one would expect to observe this effect—that is, a drug-induced modulation for weak but not for strong associations.

The present experiment was designed to test this prediction in a conditioned taste aversion (CTA) paradigm. The CTA paradigm was used because, as a one-trial learning paradigm, it allows the animals to receive only one injection for acquisition and one injection for testing, thereby avoiding problems of tolerance or sensitization that are encountered with repeated injections. CTA is a situation in which a conditioned stimulus CS (a taste) is paired with an unconditioned stimulus US (LiCl-induced sickness in the present experiment). To vary the strength of the association, the magnitude of the US was modified by changing the dose of LiCl, thereby modulating the induced illness (Nachman & Ashe, 1973). The drug selected to induce the internal cue was the noncompetitive NMDA antagonist ketamine at a nondebilitating dose (6 mg/kg). Ketamine was selected because it has been repeatedly shown to act on learning and memory processes in a state-dependent manner in a CTA paradigm (Aguado, San Antonio, Perez, Del Valle, & Gomez, 1994) as well as in an operant paradigm (Jackson et al., 1992). The typical procedure of state-dependency research was used (viz., a 2×2 design), with four conditions differing as a function of whether the subjects were conditioned under ketamine or saline and tested under ketamine or saline (Conditions Ket–Ket, Ket–Sal, Sal–Sal, and Sal–Ket). Each condition was then subdivided into five groups, each of which received a dose of LiCl ranging from 7.95 to 127.20 mg/kg.

METHOD

Subjects

One hundred sixty naive male Long-Evans rats (Janvier, France) weighing 280 ± 30 g were used. They were housed, 2 per cage, in a colony room maintained on a 12:12-h light:dark cycle (light on at 0800) with food and water provided ad lib.

Drugs

Ketamine (Imalgène, Rhône Mérieux, France) was dissolved in saline. Ketamine (6 mg/kg) and saline were injected intraperitoneally (i.p.) in a volume of 1 ml/kg of body weight.

Procedure

The animals were randomly allocated to one of two samples ($n_s = 80$), with one sample conditioned under ketamine, the other under saline. Each of these two samples was subdivided into five numerically equivalent subsamples ($n_s = 16$), according to the volume of LiCl (0.15 M) that they received: 1.25, 2.50, 5.00, 10.00, or 20.00 ml/kg (i.e., 7.95, 15.90, 31.80, 63.60, or 127.20 mg/kg, respectively). The experiment began following a series of three daily handling sessions and was conducted daily, always at about the same time.

The animals were placed on a water deprivation schedule the day before the study began. The daily drinking sessions throughout the experiment lasted 5 min and were conducted during the morning period (0900–1300 h) in a test cage ($30 \times 25 \times 35$ cm). The solutions were presented at room temperature. During the evening (1900 h), the animals were allowed access to tap water in their home cage for 20 min. The procedure lasted 11 days and was divided into four consecutive phases. During the first 7 days, the animals were shaped to drink tap water from a "Richter" tube in the test cage. On Day 8 (the conditioning day), the animals were injected with ketamine or saline 10 min prior to the experimental sessions and were then allowed to drink from this tube a sweet solution of .06% K^+ acesulfam (Sunett, Hoechst, Germany). Within 5 min after the end of the drinking session, the animals were injected i.p. with LiCl. At the end of the conditioning day, each subsample was subdivided into two groups of 8 animals, with an equal mean amount of K^+ acesulfam consumed by each group of a given subcondition. Days 9 and 10 were reshaping days, during which the animals had access to tap water. On Day 11 (the test day), each subsample was injected 10 min prior to the test session, one group being injected with ketamine, the other with saline. All the animals were then allowed to drink the sweet solution (one-bottle test).

Data Analyses

The volume consumed each day by the animals was measured to the nearest 0.5 ml. A suppression ratio was computed. For that, the volume consumed during the test day was divided by the sum of the volume consumed during the conditioning day and the test day. Thereafter, a suppression score was obtained by subtracting the suppression ratio from 1. Thus, a score of 1 indicates a total suppression of consumption during the test; a score of less than 0.5 indicates an increase of consumption during the test day, compared with the conditioning day. Data were analyzed in a two-way analysis of variance (ANOVA), with condition (4 levels) and dose of LiCl (5 levels) as between-subjects factors. The Brown-Forsythe correction was used for the ANOVA, since the variances were not equal. Post hoc analysis was performed using a Bonferroni multiple t test with alpha adjusted for 30 comparisons (i.e., 6 comparisons for each of the 5 doses of LiCl: Sal–Sal vs. Sal–Ket; Sal–Sal vs. Ket–Sal; Sal–Sal vs. Ket–Ket; Sal–Ket vs. Ket–Sal; Sal–Ket vs. Ket–Ket; Ket–Sal vs. Ket–Ket [BMDP; Dixon, 1988]). Additional trend analyses were realized for each condition, by using the method of orthogonal polynomials (Keppel, 1982).

RESULTS

Figure 1 depicts the mean score of CTA for each group. For each condition (Sal–Sal, Ket–Ket, Sal–Ket, or Ket–Sal), the suppression score increased with the dose of LiCl. With the exception of the 15.90-mg/kg dose of LiCl, all the groups exhibited a roughly similar score of CTA for a given dose of LiCl. With the dose of 15.90 mg/kg of LiCl, Group Ket–Ket displayed a higher score than the scores observed in the other groups injected with the same

Figure 1. Mean suppression score for the four treatment conditions (Sal-Sal, Ket-Ket, Sal-Ket, Ket-Sal) according to the dose of LiCl received by the rats. A score of 1.0 means a complete suppression of drinking during the test day. A score of less than 0.5 indicates an increase of drinking during the test day, relative to the conditioning day. For each value, $n = 8$. *** $p < .001$.

dose. A two-way ANOVA showed a significant effect of condition [$F(3,86) = 11.07, p < .0001$], a significant effect of doses of LiCl [$F(4,86) = 68.50, p < .0001$], and a significant interaction of condition $\times$ doses [$F(12,86) = 3.33, p < .001$]. The post hoc analysis showed that, when the four groups injected with the same dose of LiCl were compared, Group Ket-Ket injected with 15.90 mg/kg of LiCl was the only one that differed from the others [$t(140) = 6.67, 4.35, 5.48$, all $ps < .001$ for Groups Sal-Sal, Ket-Sal, and Sal-Ket, respectively].

In order to further characterize the interaction between condition and doses of LiCl, a trend analysis was separately performed on each of the four conditions. Figure 2 depicts, for each of these conditions, the individual scores of CTA and the relationship between these scores and the doses of LiCl on a semilogarithmic scale. As can be seen in Figure 2, Condition Sal-Sal exhibited little suppression of consumption at the two lowest doses of LiCl and strong suppression at the three remaining doses, the transition being located between 15.90 and 31.80 mg/kg. For this condition, the trend analysis detected a sigmoidal relationship between the log of the dose of LiCl and the effects observed [$F_{\text{quart}}(1) = 6.96, p_{\text{quart}} < .02$]. Contrastingly, Conditions Sal-Ket and Ket-Sal yielded a suppression score which increased with the dose of LiCl in a linear log relationship [$F_{\text{lin}}(1) = 54.06, p_{\text{lin}} < .0001$; $F_{\text{quad}}(1) < 1$; and $F_{\text{lin}}(1) = 75.91, p_{\text{lin}} < .0001$; $F_{\text{quad}}(1) < 1$, for Conditions Sal-Ket and Ket-Sal, respectively]. Finally, Condition Ket-Ket also exhibited a dose-dependent CTA. However, unlike in the other conditions, a quasi-ceiling effect was observed as early as 15.90 mg/kg of LiCl. Moreover, for this condition, the trend analysis indicated that the suppression score was rather different from that for the other conditions, since

a quadratic function of the log (dose of LiCl) fit the data [$F_{\text{quad}}(1) = 7.28, p_{\text{quad}} = .01$; $F_{\text{cub}}(1) = 3.64$].

DISCUSSION

The present study shows that when injected both during the acquisition and the retrieval phases, a low dose (6 mg/kg) of ketamine enhances animals' performances in a CTA paradigm. However, this enhancement is observed only for one out of the five doses of LiCl used here—namely, 15.90 mg/kg. This enhancement is thought to reflect a ketamine-induced facilitation of memory retrieval rather than any nonmnemonic process, such as an antidipsic or/and a proaversive effects of the drug. The group Ket-Ket injected with 7.95 mg/kg of LiCl exhibited the same suppression score as that of the three other groups injected with 7.95 mg/kg of LiCl, which rules out the possibility that ketamine-induced antidipsia occurred in this study. Ketamine-induced proaversive effects (i.e., ketamine had potentiated LiCl-induced effects) should have been detected equally in Conditions Ket-Sal and Ket-Ket, since all the groups in these two conditions received ketamine during the acquisition.

Our results show that ketamine-induced facilitation is only evidenced for a weak CTA. A dose of 15.90 mg/kg of LiCl is a low dosage that is not conventionally used to induce a CTA. Ordinarily, CTA paradigms use higher dosages of LiCl, generally ranging from 31.80 to 127.20 mg/kg (see, e.g., Archer, Sjöden, & Nilsson, 1985; Hall & Channell, 1986). However, 15.90 mg/kg of LiCl, as well as 7.95 mg/kg, induced CTAs—but weak ones, as is attested in Condition Sal-Sal by moderate suppression scores between .5 and .6. When they were injected with saline rather than LiCl, our animals exhibited an increase

Figure 2. Individual suppression score for the four treatment conditions (Sal-Sal, Ket-Ket, Sal-Ket, Ket-Sal) according to the dose of LiCl received by the rats. Data are presented on a semilogarithmic scale. Each dot represents the score for one rat. For each group, the solid line represents the dose relationship as determined by the trend analysis (see text for details).

of consumption during testing compared with the acquisition, with a typical score of .4. This is thought to reflect the initial neophobic response of rats against K^+ acesulfam, which is seen with most novel tastes (see, e.g., Barnett, 1958; Domjan, 1977).

Contrastingly, we did not observe ketamine-induced facilitation with strong CTA. Indeed, no significant difference was observed between Groups Sal-Sal and Ket-Ket injected with 31.80 mg/kg of LiCl; both groups displayed high suppression scores. This absence of difference cannot be attributed to a ceiling effect, because a complete suppression of drinking was observed in only 1 of the 8 rats in Group Ket-Ket. The latter result argues against the fact that ketamine-induced facilitation observed with 15.80 mg/kg of LiCl could result from the potentiation by the taste of an aversion to ketamine, as has been reported with, for example, taste-odor combinations (see, e.g., Rusiniak, Hankins, Garcia, & Brett, 1979).

The trend analysis showed that the results displayed by the five Ket-Ket groups could be described with a quadratic function. This suggests that the facilitation observed at 15.90 mg/kg of LiCl is not erratic, but rather belongs to a continuum of effects. When one considers Condition Sal-Sal, the transition between a weak and a strong CTA is located just beyond 15.90 mg/kg of LiCl. This suggests that ketamine-induced facilitation is, in fact, a shift toward the lowest doses of LiCl in comparison with what is observed in a traditional CTA—that is, in the condition Sal-Sal—as if, in the presence of a stable cue (viz., ketamine), the animals had a more sensitive representation of the US or of the CS-US association. This is precisely how external contextual cues are believed to act during retrieval. As a matter of fact, Konorski

(1967), Medin (1975), and Spear (1973) have suggested that the external training context “facilitates” retrieval of association between the nominal CS and US; that is, the presence of the external conditioning context during testing enhances the effectiveness of the CS in eliciting conditioned responding. More precisely, Medin (1975) and Spear (1973) hypothesize that the context serves as a cue for the retrieval of associations to the CS as the result of its being an attribute of the target memory system (see also Miller & Matzel, 1988; Miller & Schachtman, 1985). Nadel and Willner (1980) advocate a similar view—specifically, that a hierarchical relationship of cues exists in which contexts both contain and predict CSs.

To summarize, the present study suggests that ketamine-induced facilitation parallels the facilitation observed with external contextual cues. Indeed, ketamine is used by subjects to index learning, and such indexing facilitates retrieval under the following conditions. First, facilitation is observed when the strength of the association between stimuli is low; second, ketamine must be present during both the acquisition and the test phases to be efficient.

Besides facilitation, in the present study we did not observe ketamine-induced SDR. Whenever a shift of state (Sal-Ket or Ket-Sal) between the acquisition and the retrieval phases occurred, we observed a suppression score similar to the one observed in Condition Sal-Sal. A dose of 6 mg/kg of ketamine is probably too low to allow us to observe SDR in a CTA paradigm. Indeed, on the one hand, Jackson et al. (1992) found evidence for SDR with a similar dose range, but with animals experiencing several days of training under ketamine. On the other hand, Aguado et al. (1994) found evidence for SDR in a one-

trial CTA paradigm, but with a high, debilitating dose of 25 mg/kg of ketamine. This suggests that a one-trial predisposed type of learning such as CTA is probably poorly sensitive to changes of state and therefore requires massive dosages to exhibit clear drug-induced SDR. Nevertheless, in our conditions, 6 mg/kg of ketamine may have impaired memory processes in an SDR manner, but this impairment may have been too weak to affect our results significantly. As a matter of fact, the trend analyses detect a qualitative differential LiCl-induced dose relationship for Condition Sal-Sal (a sigmoidal one) and for Conditions Sal-Ket and Ket-Sal (linear ones). When one considers the individual suppression scores, it appears that the linear relationships observed were due to the wide dispersion of the performances at 31.80 mg/kg of LiCl for Groups Ket-Sal and Sal-Ket, with half of the animals in each of this two groups exhibiting lower suppression scores than the lowest score observed in Group Sal-Sal. This qualitative difference leads us to propose that, at least with ketamine, facilitation and SDR might reflect a continuum of similar memory processes, with drug-induced facilitation being observed with lower dosage than that for drug-induced SDR. In the former case, the drug would be used as a discrete cue, facilitating the retrieval of the target information that has been weakly processed. In the latter case, because of the higher dosage, the drug would lock the target information in the drug state, even when it was more deeply processed, requiring the subject to experience this state to retrieve it. Increasing the processing for this information (by overtraining, for example; see, e.g., Iwahara & Noguchi, 1972, 1974) will unlock the memory trace from the drug state, allowing the subject to retrieve the information, whatever the present state.

In conclusion, the present results are consistent with the notion that drug-induced SDR is a contextual phenomenon. However, they stress that drug-induced contextual effects should vary according to two distinctive dimensions: a pharmacological one—that is, the dosage of the drug used—and a psychological one—that is, the amount of processing for the target information. This could be an important difference for the way in which drug stimuli and exteroceptive sensory stimuli control learning or retrieval processes. In particular, this could account for the fact that, unlike exteroceptive stimulus control, SDR is so inconstantly observed from one study to another (see, e.g., Aguado et al., 1994, vs. Welzl, Alesandri, & Bättig, 1990).

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