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Short communication

Paradoxical effects of ketamine on the memory of fetuses of different ages☆

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Abstract

Brain *N*-methyl-D-aspartate (NMDA) glutamate receptors have been implicated as important mediators of both learning and neuronal development. The current study investigated how ketamine (a well-known NMDA-receptor blocking drug) influences taste-mediated conditioned motor responses (CMRs) in perinatal rats. Dams pregnant with either embryonic day 18 (E18) or E19 rat fetuses were injected with 0 or 100 mg/kg ketamine HCl (i.p.). One-half hour later, a reversible spinal block was performed on the dam and fetuses received oral lavage with 10 μl, 0.3% saccharin (SAC) or water (control) in utero. After the oral injection, fetuses received either a saline (control) or lithium chloride (LiCl) injection (81 mg/kg, i.p.). The uterus was replaced and, 2 days later (E20 or E21), some rats received oral lavage with SAC. Other litters were born via normal vaginal delivery or Cesarean section and orally exposed to SAC on post-natal day 3 (P3). Motor responses were observed immediately after the oral lavage of SAC. If SAC had been paired with LiCl in utero, pups generally exhibited conditioned suppression of orofacial movements (as compared to controls). Ketamine significantly attenuated this taste-mediated CMR of animals conditioned on E19. However, the same treatments did not disrupt CMRs of rats treated with ketamine before CS–US pairing on E18. Our findings indicate an age-dependent role for NMDA receptors in the formation of CMRs in perinatal rats.

Theme: Neural basis of behavior

Topic: Learning and memory: pharmacology

Keywords: Conditioned taste aversion; Fetus; Neonate; Rat; Memory; Saccharin; Lithium chloride; Development; Ketamine; NMDA; Learning; Ketamine paradox

Rats may acquire taste-mediated conditioned motor responses (CMRs) in the perinatal period. Pairing oral lavage of a chemical stimulus with an intraperitoneal (i.p.) injection of LiCl on E17, E18 or E19 creates conditioned suppression of rat fetal activity when subjects were re-exposed to the same stimulus 2 days later [17,26,27].

Our previous studies have shown that blockade of glutamate *N*-methyl-D-aspartate (NMDA) receptors altered memory formation of perinatal rats in an age-dependent manner. Administration of ketamine (a well known NMDA receptor blocker) [5,28] before CS–US pairings potentiated a conditioned taste aversion (CTA) in E18 fetuses [13]. However, when injected with equivalent doses of ketamine, P0 neonates later failed to exhibit a CTA [14]. These data are remarkable since ketamine usually disrupts performance on a variety of learning and memory tests (including CTA) in adult rats [1,2,8,29,31]. Thus, there may be critical periods in the developmental process when NMDA receptor blockade can produce very different effects on learning and memory.

The current studies were aimed at discerning when, during the perinatal period, ketamine switches from a memory enhancer to a memory blocker. Here we report

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that the CMR of ketamine-treated fetuses conditioned on E18 is preserved while these same responses are blocked if ketamine is administered before a CS–US pairing on E19.

The subjects were fetal and neonatal Sprague–Dawley rats (male and female) obtained from timed-pregnant dams supplied by Zivic-Miller Laboratories (Zelienople, PA, USA). Pregnant animals (from which our subjects were derived) were individually housed in plastic 'shoe box' cages (44.45 cm long×21.59 cm wide×20.32 cm high). Home cage temperature was maintained at 23–26°C under a 12/12 h light–dark cycle starting at 06:00 h.

Studies of CTA typically involve a conditioning trial, latent period, and subsequent test for retention. In order to avoid confounds induced by requiring subjects to remember conditioned responses for variable periods we used a standard 2-day conditioning-test latency for rats of different ages. Throughout this manuscript, these animals are referred to as 'latency-constant' groups. Specific references are made to E18–E20 or E19–E21 (conditioning age–testing age) animals. We employed additional animals on a different training-test schedule to keep constant their age at time of testing. Animals in these 'age-constant' groups were tested on P3 independent of conditioning on E18 or E19. These groups of animals are referred to as E18–P3 and E19–P3. See Table 1 for the complete outline of experimental design and numbers of subjects in each group.

One-half hour before fetal injections began (see below), pregnant dams received injection of either 100 mg/kg ketamine HCl (Sigma), i.p. or equal volume of physiological saline. This dose of ketamine was selected based on data from previous experiments [13,14]. Other studies have shown that a maternal dose of 50 mg/kg ketamine is less effective in producing effects reported here [18].

Fetal injections and fetal/neonatal behavioral testing were conducted as described previously [16,17]. Pregnant dams were temporarily anesthetized with Isoflurane™ before undergoing a reversible spinal block procedure. The analgesic dam was restrained in a plastic holding apparatus and her vision of the procedure restricted. Uterine horns were exposed through midline laparotomy and the hind legs and lower abdomen immersed in a warm bath (37.5±1°C) containing isotonic saline (Locke's solution) [7]. Both uterine horns were exteriorized through the abdominal incision and allowed to float freely in the bath. All fetuses in a particular litter received oral lavage of either the conditioned stimulus (CS=10 μl 0.3% saccharin, SAC) or a control vehicle injection (10 μl distilled water) through the uterine wall. Fifteen minutes following CS administration, rats received i.p. injection of the unconditioned stimulus (US=81.0 mg/kg LiCl) or a control vehicle injection of saline. Thus, three combinations of injections defined our main treatment groups: (1) SAC+LiCl: the main taste aversion conditioning group; (2) SAC+Sal: controls for the non-conditioned effects of the CS alone; (3) water+LiCl: controls for the non-conditioned effects of the US. Following injections, the uterus was replaced, the abdominal wall and the skin of the dam sutured, and wounds infused with local anesthetic (bupivicaine; 0.25%) to produce post-surgical analgesia. For fear of mixing chemical stimuli among fetuses, all pups in the same litter received the same treatments. This procedure necessitated special data analysis techniques (see later).

If fetuses were tested on E20 (i.e., E18–E20 subjects), dams were provided analgesia using an irreversible spinal block (0.1 ml 100% ethanol) via the general method described above. Both uterine horns were exteriorized through the abdominal incision, and allowed to float freely in the Locke's bath. Fifteen minutes were allowed to elapse before onset of behavioral observations, to allow the dam and fetuses to recover from Isoflurane™ anesthesia used during the spinal block procedure. Still attached to the dam via umbilical cords, fetuses were removed from the uterus and floated in the Locke's bath. A 20-gage stainless steel injection tube was placed in each fetus's mouth and 10 μl SAC injected into the oral cavity. Behavior was videotaped for 1 min immediately before (baseline) and after oral SAC injection.

All rats in the E19–E21, E18–P3 and E19–P3 groups were tested as neonates. If rats had not been born 4 h before the scheduled behavioral test on E21, they were removed by Cesarean section. Sixteen of the 23 E19–E21 litters experienced this procedure. Cesarean section was

Table 1
Experimental design and number of subjects (litters) in each group

Latency/age-constant groups	Drug treatments[a]					
	Saline			Ketamine (100 mg/kg, i.p.)		
	SAC+LiCl[b]	SAC+saline	Water+LiCl	SAC+LiCl	SAC+saline	Water+LiCl
E18–E20[c]	14 (3)	13 (3)	15 (3)	16 (4)	15 (4)	14 (4)
E19–E21	19 (5)	17 (4)	12 (2)	18 (4)	20 (5)	14 (3)
E18–P3	11 (3)	14 (4)	12 (2)	13 (3)	12 (6)	10 (5)
E19–P3	11 (3)	10 (2)	15 (5)	14 (3)	17 (4)	14 (4)

[a] Drug treatments were administered to pregnant dams 30 min before conditioning.
[b] SAC=10 μl 0.3% saccharin oral lavage (CS); LiCl=lithium chloride (81 mg/kg, i.p.) (US); control injections of water or saline were also administered.
[c] First embryonic (E) age indicates post-insemination conditioning day; second embryonic or postnatal (P) day represents behavioral testing age.

accomplished while the dam was provided analgesia via irreversible spinal block (0.1 ml 100% ethanol) using the procedure described above. For behavioral observations, neonates were placed in a warm (28±1°C), high-humidity chamber on a glass plate warmed (via circulating water) to 36±1°C. Pups received oral lavage with 10 μl SAC through a blunt 18-gage stainless steel infusion needle. Subjects were then placed (ventral side down) on the glass plate. Using a mirror, behavior was videotaped from below the animal as described previously.

Videotaped behaviors were later reviewed by a practiced observer and scored using The Observer™ software (Noldus Information Technology). Using a modification of the methods described by Smotherman et al. [25], we sorted observed behaviors into 12 categories of spontaneous fetal/neonatal movements. Because they seemed the most sensitive indicators of CMRs, this paper focuses on orofacial movements: a combination of mouth movements and licks. The interrater reliability of behavioral scoring is high ($r=0.91$).

Neonates born via Cesarean section exhibited mouthing and licking responses statistically indistinguishable from those of pups that underwent normal vaginal delivery. Therefore, the data from Cesarean and vaginally born animals were combined in all analyses reported. Likewise, preliminary analyses revealed that the subjects in the two control groups (SAC+Sal, water+LiCl) did not differ significantly from one another, and the animals were pooled and treated as 'combined controls'.

One group was tested as fetuses (E18–E20) while the other groups were tested using the neonatal procedure. Previous control experiments have demonstrated that, following oral lavage with SAC, E20 fetuses show orofacial motor responses similar to those seen in E21 neonates [16]. Still, comparisons of different aged rats may be challenged by the fact that quantity of spontaneous movement generally increases as rats move through the perinatal period. In an attempt to control for differences in level of overall activity demonstrated in the fetal vs. neonatal testing situation, our treatment of the data included an initial analysis of covariance. Here we used as a covariate each animal's total activity (a total of head, mouth, lick, gape, curl, stretch, twist, roll, hindlimb, forelimb, facewipe, and twitch movements) [25] during the baseline period. Each dependent variable was analyzed through a three-way Analysis of Covariance (ANCOVA) of the form: Age (E18–E20 or E19–E21)×Drug (0 or 100 mg/kg ketamine)×Treatment (Sac+LiCl or combined controls). Similar ANCOVAs were employed to evaluate the behavior of age-constant animals. We used a linear model (SAS™, SAS Institute, Carey, NC, USA) compensating for unequal n values. If the covariate effect was not statistically significant ($P>0.05$) then subsequent analyses of variance (ANOVAs) were run without the covariate.

Since all rats in a particular litter received the same conditioning treatment, we included litter as an independent, random, nested factor (within conditioning treatments). This approach controlled for litter effects and offered a direct statistical test of the significance of such effects [6,10]. However, effects attributable to litter were not statistically significant and therefore subsequent analyses were run without this factor. Post hoc analyses employed Duncan's Multiple Range Test [12]. An $\alpha=0.05$ was adopted throughout these tests.

An injection of LiCl causes a reduction in spontaneous activity [26] in fetal and neonatal rats. The current studies corroborate those of Smotherman and Robinson [26] (see Ref. [27] for review) who demonstrated that a single pairing of a taste CS with LiCl can produce conditioned suppression of orofacial movements when the animal is later re-exposed to the CS. Further, our data indicate that if ketamine is administered before CS+US pairing, it can influence CMRs in an age-dependent manner. Specifically, the same dose of ketamine that blocks CMRs acquired by E19 rat fetuses fails to disrupt CMRs developed in E18 fetuses. We refer to this phenomenon as the 'ketamine paradox'.

The three-way ANOVA of the mouthing and licking responses of E18–E20 and E19–E21 rats revealed a significant Age effect [$F(1,179)=74.16$, $P<0.01$], a significant CS–US Treatment effect [$F(1,179)=6.67$, $P<0.01$], a significant Treatment×Drug interaction [$F(1,179)=7.67$, $P<0.01$], and a significant Age×Treatment×Drug interaction [$F(1,179)=7.05$, $P<0.01$]. Post hoc analyses showed that oral lavage with SAC on the test day produced a conditioned suppression (as compared to controls) of mouthing and licking in both E18–E20 and E19–E21 animals treated with saline before the initial CS+US pairing (Fig. 1). E18 fetuses pre-treated with ketamine maintained a significant CMR when tested on E20. However, E19 animals that received ketamine failed to show significant conditioned suppression of mouthing and licking movements on E21. Ketamine's effects on the formation of CMRs appear to be age-dependent.

Age-constant groups (E18–P3; E19–P3) required to maintain a CMR over a 5–6 day period exhibited the ketamine paradox – but less dramatically. The three-way ANOVA comparing the mouthing and licking responses of E18–P3 and E19–P3 rats revealed a significant CS–US Treatment effect [$F(1,145)=7.61$, $P<0.01$] and a significant Drug effect [$F(1,145)=3.86$, $P<0.05$]. Groups of saline-treated rats conditioned on E18 and E19 significantly reduced their mouthing and licking following oral lavage of SAC on P3 (Fig. 1). Ketamine blocked the CMRs of E19–P3 neonates. However, E18 rats pre-treated with ketamine and SAC+LiCl continued to show conditioned suppression of mouthing and licking following oral lavage with SAC on P3.

The experiments reported here confirm previous indications of a paradoxical, age-dependent effect of ketamine on learning. Prior studies suggested that ketamine (100 mg/kg, i.p. delivered to the dam) potentiated CTA established

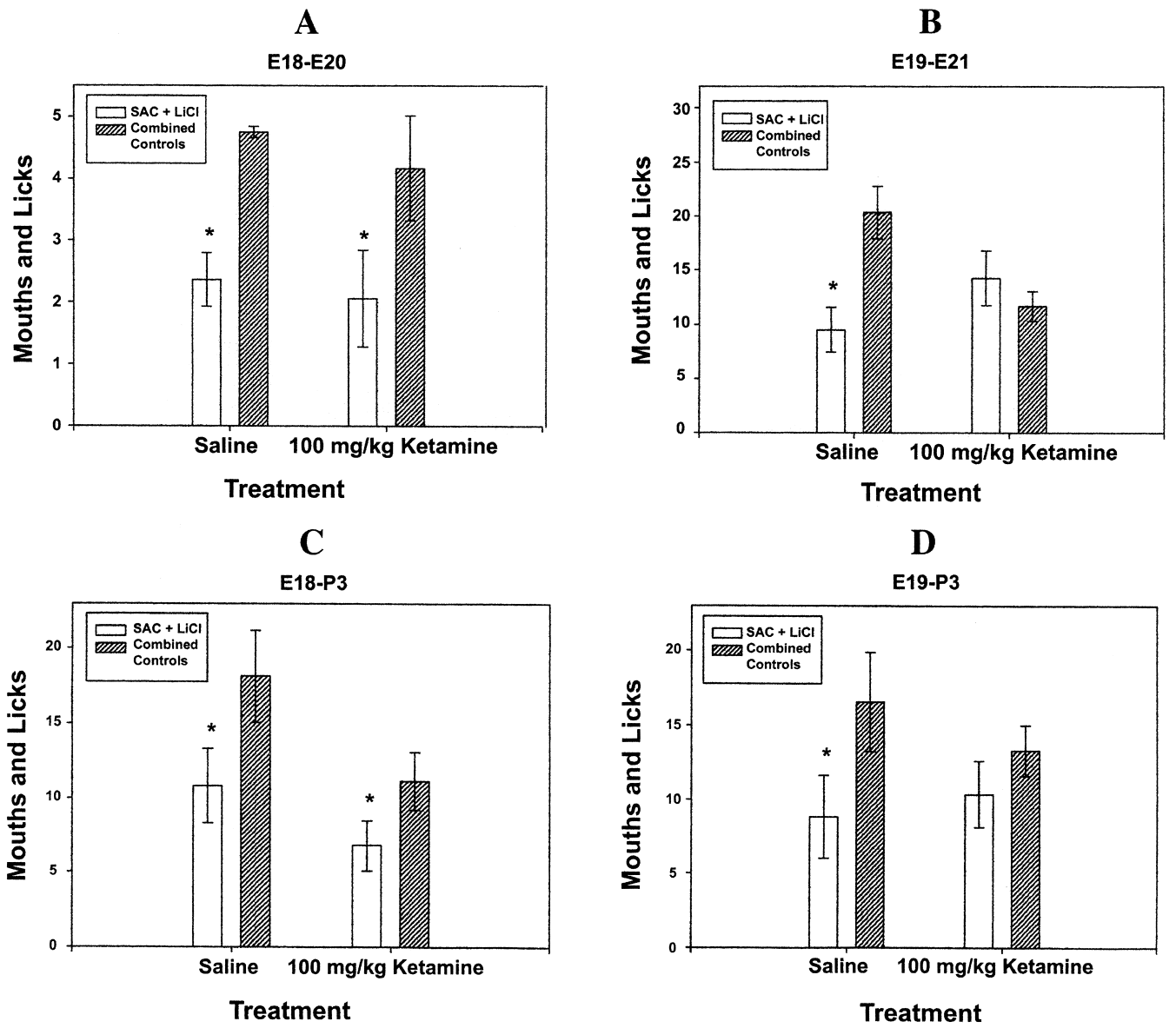

Fig. 1. Mean number of mouthing and licking responses following exposure to SAC. Fetuses aged E18 (panels A & C) or E19 (panels B & D) received a single pairing of SAC (10 μl, 0.3% saccharin delivered orally) and LiCl (81 mg/kg lithium chloride, i.p.) or a set of control injections (see text for methods) and were observed either 2 days later (panels A or B) or on P3 (panels C & D) following a taste of SAC. Fetuses receiving saline before SAC+LiCl pairing exhibited conditioned suppression of mouthing and licking movements when re-exposed to SAC. Exposure to ketamine before SAC+LiCl conditioning blocked this response in pups conditioned on E19. However, ketamine failed to disrupt conditioned responses in rats trained on E18. *=Significantly different ($P<0.05$) from combined control group. Variance measures are the S.E.M.

in E18 rat fetuses [13], but an equivalent dose of the drug blocked CTAs in P0 neonates [14]. In early experiments neonatal avoidance of SAC-painted nipples was recorded as an indicator of CTA. In the current studies we evaluated the generalizability of the ketamine paradox by investigating CMRs. These data not only indicate that the paradox may be observed in a variety of behavioral contexts, but also suggest that ketamine's effects on memory change between E18 and E19. These data are similar to those found in a preliminary report suggesting that ketamine can enhance measures of conditioned perseverative responding when administered on E18, while blocking this response in E19 rats [18].

We have explored possible alternative, non-associative explanations for these findings. Could our data be produced by ketamine-induced alteration of gustatory or visceral sensation of SAC or LiCl? The plausibility of this explanation is weakened by evidence suggesting that NMDA receptors do not play a prominent role in mediating sensory aspects of taste or malaise [4,15]. Ketamine

and other NMDA antagonists do not disrupt habituation to the neophobia observed upon exposure to a novel taste [1,22]. On the other hand, the kinetics and metabolism of SAC, LiCl and ketamine in fetuses of different ages has not been fully explored but may ultimately provide insights regarding the ketamine paradox. The interplay of fetal/maternal drug kinetics, taste habituation, and amniotic fluid clearance rates were discussed in a previous paper [16]. However, it should be noted that data speaking directly to this issue are not currently available.

A possible explanation for these paradoxical effects of ketamine administration at different times during the perinatal period may be sought in studies of NMDA receptor development. NMDA receptor populations and physiology are neither static nor mature during the perinatal period [3,9,24]. These data build on previous findings [23] indicating dramatic changes in the number of PCP-binding sites in fetal rat brain between E18 and E19. Could these developmental changes in NMDA receptor populations and functional roles mediate the ketamine paradox? If particular NMDA receptors or subtypes are either immature or non-functional prior to E19, then injecting ketamine on E18 may have little pharmacological effect on behavior. If so, the 'ketamine paradox' may be better characterized as a developmental phenomenon. Further identification of NMDA receptor subtypes with different functions and expressive patterns during the perinatal period [19–21,30,32] may reveal the physiological substrates of the behavioral data we report here.

The possibility of developmentally-linked and rapidly changing roles for brain NMDA receptors is conceptually consistent with recent findings from other laboratories. Kakizawa et al. [11] reported that blockade of NMDA receptors during P15–16 resulted in higher incidence of climbing fiber innervation from cerebellar Purkinje cells and persistent alterations in motor coordination. Our data point to an earlier 1-day window when functional shifts occur due to NMDA receptor blockade.

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