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Behavioural alteration in the progeny of rats exposed to ketamine, a n-methyl-d-aspartate receptor blocker

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Introduction

The aim of the present study was to obtain further information on the possible adverse effects of ketamine on cognitive functions. Ketamine is a phencyclidine-like dissociative anaesthetic which binds to a phencyclidine site in the N-methyl-D-aspartate (NMDA) receptor gated ion channel and inhibits the NMDA subtype of glutamate receptors in a non-competitive manner. Previous studies have demonstrated that exposure to ketamine hydrochloride may result in impaired cognitive behavioural and motor functions in rats (*Øye et al.* 1993, *Lalonde & Joyal* 1993, *Pallares et al* 1995, *Murata & Kawasaki* 1993, *Silvestre et al.* 1997), mice (*Irifune et al.* 1995, *Kim et al.* 1996) and guinea pigs (*Jerram et al.* 1996). In rabbits, high doses of ketamine (100 and 200 mg/kg) were shown to block the display of conditioned responses (*Ghoneim et al.* 1994), whereas in cats ketamine at doses of 2-10 mg/kg was demonstrated to modulate the habituation of the response to visual stimulation in the superior colliculus (*Binns and Salt* 1995). In humans, ketamine at subanaesthetic doses was shown to produce decrements in free recall, recognition memory, and attention in healthy volunteers (*Malhotra et al.* 1996), result in dose-dependent amnesia in patients receiving high doses for pain control in intensive care units (*Wagner et al.*1997), and to induce exacerbation of psychotic symptoms and cognitive impairment in schizophrenics (*Malhotra et al.* 1997) as well as a decline in memory and verbal fluency in Huntington patients (*Murman et al.* 1997). On the other hand, LaPorte et al. (1996) reported that they could demonstrate no impairment either in memory tasks or in other cognitive functions in schizophrenia patients. Most of these animal and human studies were conducted in young adults and grown-up individuals, whereas one would expect that effects on CNS function would be most pronounced following exposure during the sensitive developmental stages in fetal and early postnatal life. We have previously reported effects on conditioned behaviour in the progeny of rats administered ketamine during pregnancy and lactation (*Øye et al.* 1993), but not in rats given ketamine during pregnancy only. In the present investigation, the first study was conducted with the administration of ketamine to rats during pregnancy, both pregnancy and lactation, and lactation, respectively, in order to localise the most sensitive period for behavioural effects of ketamine. In the second study pups were injected subcutaneously with ketamine from day 4 of age to day 19 postnatally.

Various instrumental conditioning learning problems besides increased or decreased motor activity have been reported in rats and mice following exposure to ketamine. The procedure of visual discrimination in a Skinner box was considered appropriate in this investigation because operant methods are considered sensitive tools for the detection of behavioural changes (*Branch* 1991). The advantage of these test procedures is associated with their ability to characterise the functional significance ofketamine from a coherent systematic approach (*Laties & Wood* 1986). In addition, comparative research is possible because the behavioural laws seem to be similar in animals and humans (*Matthews et al.* 1977; *Sagvolden et al.* in press).

Materials and Methods

The studies were conducted in the Laboratory Animal Unit at the Norwegian College of Veterinary Medicine. The animals were fed a commercial pelleted diet (Ewos, Södertälje, Sweden), and were housed in animal rooms with temperature 21 +/- 1°C and relative humidity 40 to 60 %. The light cycle was 12:12 light dark.

In the first study, 24 albino Lewis rats (Møllegaard Breeding Centre, Ejby, Denmark), all mated on the same night, were randomised into two groups of 12 animals and housed individually in Macrolone Type 3 cages. One group was injected subcutaneously with ketamine 3 mg/kg two times daily from day 7 of gestation. The other group received subcutaneous injections of saline at corresponding volumes. Both groups were treated up to gestation day 21, the day before delivery. Four ketamine-treated and 6 saline-treated dams proved not be pregnant. The dose of ketamine chosen was the highest dose that did not produce symptoms of intoxication in a preliminary study performed. Therefore higher doses were not appropriate for behavioural testing.

The litters of ketamine-treated mothers were randomised into two groups of 4 litters per group and the litters of saline-treated mothers were randomised into two groups of 3 litters per group. From postnatal day 3, the four litter groups were subjected to the following treatments:

One litter group (preg), originating from the ketamine-treated mothers, did not receive any further treatment except that their mothers received saline injections two times daily at volumes corresponding to those of the ketamine injected ones. The second litter group (lac), originating from saline-treated mothers, received ketamine through their mother's milk by means of subcutaneous injections of ketamine 3 mg/kg two times daily to the dams up to day 17 of lactation. The third litter group (preg/lac), originating from ketamine-treated mothers, received ketamine through their mother's milk by the same procedure as the lac group. The fourth group (control), originating from saline-treated mothers, received no treatment except from daily saline injections to their mothers like the preg group.

At weaning at 4 weeks post partum, 10 male pups were picked randomly from each group for behavioural training in Skinner boxes. All animals, both dams and offspring, were weighed daily during the whole treatment period, and later on, they were weighed once weekly. The pups were inspected daily for physical development.

In the second study, 5 albino Lewis rats (Møllegaard Breeding Centre, Ejby, Denmark), all mated on the same night, were allowed to litter. Sixteen male pups from the litters were randomised into two groups of 8 animals. One group (inj) was injected subcutaneously with ketamine 3 mg/kg daily from day 4 until day 19 postnatally. The other group (control) was similarly injected with the corresponding volumes of saline for the same period. Both groups were observed for physical development and were subjected to behavioural training in Skinner boxes from weaning at 4 weeks. The pups were weighed daily during the treatment period and then once weekly.

Physical signs, early movement, and neuromuscular development of each pup were examined by standard tests for rodents (*Alder* 1983) every morning during the lactation period of four weeks. Examination for physical signs included the observation of weight gain, the occurrence of downy hair, and the appearance of eye lid separation. Early movement examination included the occurrence of head lifting from the surface, and the ability to walk more than 10 steps with the abdomen lifted from the surface. Neuromuscular development was examined by testing the occurrence of grip strength of the front legs of the pups when holding them resting in the palm of the experimenter with the pup's head between the experimenter's thumb and index finger and slowly moving the hand from a horizontal to a vertical position.

Four identical Campden Instrument operant test chambers for rodents Model 4109 (Campden, UK) were used for the testing in Skinner boxes. Each chamber was located in a sound-resistant cubicle. A liquid dipper delivered a 0.01 ml drop of tap water in a small compartment separated from the test chamber with a transparent plastic lid (7 x 5 cm). A light pushing by the nose or the paw opened the lid, which activated a microswitch and made the water available for 2 s. The animal's working space was equipped with two retractable levers, a speaker presenting continuous masking noise, and two cue lamps, one above each lever.

Two lamps, one in the roof and one at the top of the intelligence panel, illuminated the working chamber during testing. The experiment was controlled by an on-line system (SPIDER E extension to BBC BASIC equipped with a 16-RAM memory card, obtained from Paul Fray Ltd., UK). This system scheduled reinforcements and recorded data into individual files.

The training program was conducted every morning 5 days a week. The rats were water-deprived for 21.5 h before the daily training during the whole test period, apart from 18 h before the magazine training. During the first 5 sessions of the program, the rats were habituated to the operant chambers at 10 min a day. The house light was on, the water was not operated, and both levers were retracted. Magazine training was conducted during 5 sessions of 10 min each. The house light was on and both levers were retracted, whereas the tray was lit and water available for periods of 5 s alternating with dark periods of 20 s with no water. During the magazine training the rats learned to find the water. Response shaping was performed in 2 sessions in which the experimenter manually operated the water delivery each time the rats pressed the lit lever. During the response shaping the rats learned the connection between lever pressing and water delivery.

The discrimination training was designed as a visual discrimination program of 45 sessions in the first study and 42 sessions in the second study, each session lasting for 10 min. The rats were taught to press the correct lever, which was indicated by the cue lamp. Pressing the correct lever was reinforced according to random ratio schedules. The tray was lit and the rats were allowed 5 s to reach the water dipper and 2 s to collect the reinforcement. In the first sessions (10 and 7 sessions in the 1st. and 2nd. studies respectively), reinforcement was given at all correct lever presses. In the next sessions, the number of reinforcements given at correct lever pressures was gradually lowered, thus presenting gradually a more demanding task in succeeding to obtain the reinforcement. Reinforcements were given randomly at an average of respectively 50 % of correct responses (9 and 7 sessions in the 1st. and 2nd. studies respectively), 25 % of correct responses (10 sessions in both studies), and 10 % of correct responses (16 sessions in the first study and 18 sessions in the second study). The schedule was changed when relatively stable performance results occurred. The criterion for changing schedule was that all the animals in each group performed more than 50 percent correct lever presses in at least 3 successive sessions. The number of total lever presses, the percent of correct lever presses, the total number of tray visits, the percent of correct tray visits, and the number of perseveration 1 type of error were recorded. The perseveration 1 type of error appeared when the animal returned to the same but now incorrect lever after having collected a reinforcer.

The data of body weights and litter size were analysed for significant differences between groups ($p<0.05$) by the Dunnett's method and the Student's t method. The behavioural data were examined for significant differences between groups ($p < 0.05$), using the mean of the 5 last sessions by Student's t-test using the NCSS (Number Cruncher · Statistical System) and the results are presented as figures.

Results

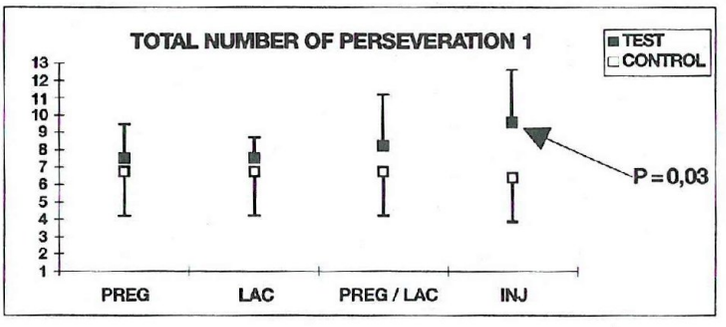
The parameters recorded for physical signs, early movements and neuromuscular development were similar for ketamine- and saline-exposed pups in each study. However, some differences between the two studies were observed. On average, the coat of downy hair and the development of grip strength appeared at the age of 6 days for the pups in both studies.

No statistically significant differences between groups were observed with respect to body weights at start and end of the Skinner box period for the pups in either study.

Because there were no significant differences between groups during the 100 %, 50 % and 25 % reinforcement schedules, only the results from the 10 % reinforcement schedule are presented.

For the perseveration error type, there was a trend towards increased number of errors in all the ketamine-treated groups of both studies as compared to their respective control values (Fig. 1).

Figure 1. Total number of perseveration 1, mean ± SEM of five last sessions, for each test group and control group.



Study 1

In the first study, when the pups were exposed to ketamine prenatally (preg), postnatally through mother's milk (lac), or both pre- and postnatally through mother's milk (preg/lac), no statistically significant effects on litter size, neonatal weight or postnatal weight gain were observed (Table 1).

Average time points for separation of the eye lids were 16 days for the pups of Study 1.

The behavioural activity, as expressed by the total number of tray visits in each session tended to be increased, although not statistically significant, in the test animals exposed to ketamine both pre- and postnatally (preg/lac) as compared to the control group in Study 1 (Fig. 2C). The pups in the groups exposed to ketamine either during pregnancy (preg) or during lactation (lac) in Study 1 showed mainly similar performance as control rats (Fig.2 A, B). The differences as compared to the control values were, however, not statistically significant.

No effect of ketamine treatment was found on total number of lever presses in Study 1.

The percentage of correct tray visits exhibited tended to be decreased in Study 1 for the animals exposed to ketamine during lactation (lac) and especially for those exposed during both pregnancy and lactation (preg/lac) as compared to control values during the last 5 sessions ($p=0.08$, Fig. 3).

Study 2

In the second study, when the pups were exposed to ketamine by direct injections (inj), no significant effects on neonatal weight or weight gain were observed as compared to the saline-treated group (Table 2).

Average time points for separation of the eye lids were 14 days for the pups of Study 2.

All pups in Study 2, independent of treatment type, developed early movements later, and separated their eye lids earlier than all pups in Study 1. On average, the pups in Study 2, were able to lift their head and to walk at day 10 and 13, respectively, compared to the pups of Study 1 where those abilities occurred at days 8 and 11, respectively. Average time points for separation of the eye lids were 14 days for the pups of Study 2.

The activity as expressed by total number of lever presses in each session tended to be increased above control values in pups exposed to ketamine by postnatal injections in Study 2 (Fig.4).

The pups in the groups exposed to ketamine by injection (inj) in Study 2 showed mainly similar performance as control rats (Fig. 2 D). The activity as expressed by total number of lever presses in each session tended to be increased above control values in pups exposed to ketamine by postnatal injections in Study 2 (Fig. 4). The differences as compared to the control values were, however, not statistically significant. The percentage of correct lever presses tended to be decreased in Study 2 for the ketamine-injected animals as compared to control values during the last 5 sessions ($p=0.07$, Fig. 5). The remaining groups showed mainly similar performance to the control values for correct tray visits and correct lever presses. On comparing the mean values the last 5 sessions for the perseveration error type, there was a

Table 1. Body weight, body weight gain and litter size of rats exposed to ketamine during day 7-21 of pregnancy (preg), during day 3-17 of lactation (lac), during both pregnancy and lactation (preg/lac) and control rats without ketamine exposure. The treatment was 2 daily s.c. injections of dams with ketamine (3 mg/kg) or corresponding volumes of saline only. Mean weights ± standard error of the means are presented. The experimental groups were compared to the control group using Dunnett's method (p=0.05).

	Preg	**Lac**	**Preg/lac**	**Control**
No. of dams	4	3	4	3
Weight of dams				
day 7 of preg.	190 ± 5	196 ± 8	196 ± 7	195 ± 5
Weight gain of dams				
day 7 to 21 of preg.	82 ± 4	103 ± 6	85 ± 2	92 ± 3
No. of pups/litter				
day 3 post partum	9.3 ± 1.3	11.3 ± 1.2	8.5 ± 1.5	8.7 ± 0.3
Mean weight of pups				
3 post partum	7.0 ± 0.2	6.7 ± 0.3	6.3 ± 0.5	7.0 ± 0.3
Mean weight gain of pups				
day 3 to 17 post partum	21.9 ± 0.3	21.0 ± 1.0	20.2 ± 1.2	21.7 ±0.5
Weight of dams				
day 17 post partum	253 ± 8	264 ± 7	247 ± 9	257 ± 8
No. of pups to Skinner box	10	10	10	10
Weight of pups day 35				
post p., start Skinner box	103 ± 1	97 ± 2	100 ± 2	103 ± 1
Weight of pups day 120				
post p., end Skinner box	328 ± 3	315 ± 5	326 ± 5	327 ± 5

Figure 2.. Total number of tray visits in each session. A: Pups exposed to ketamine prenatally (preg). B: Pups exposed to ketamine through mother's milk (lac). C: Pups exposed to ketamine both prenatally and through mother's milk (preg/lac). D: Pups exposed to ketamine by direct injections (inj).

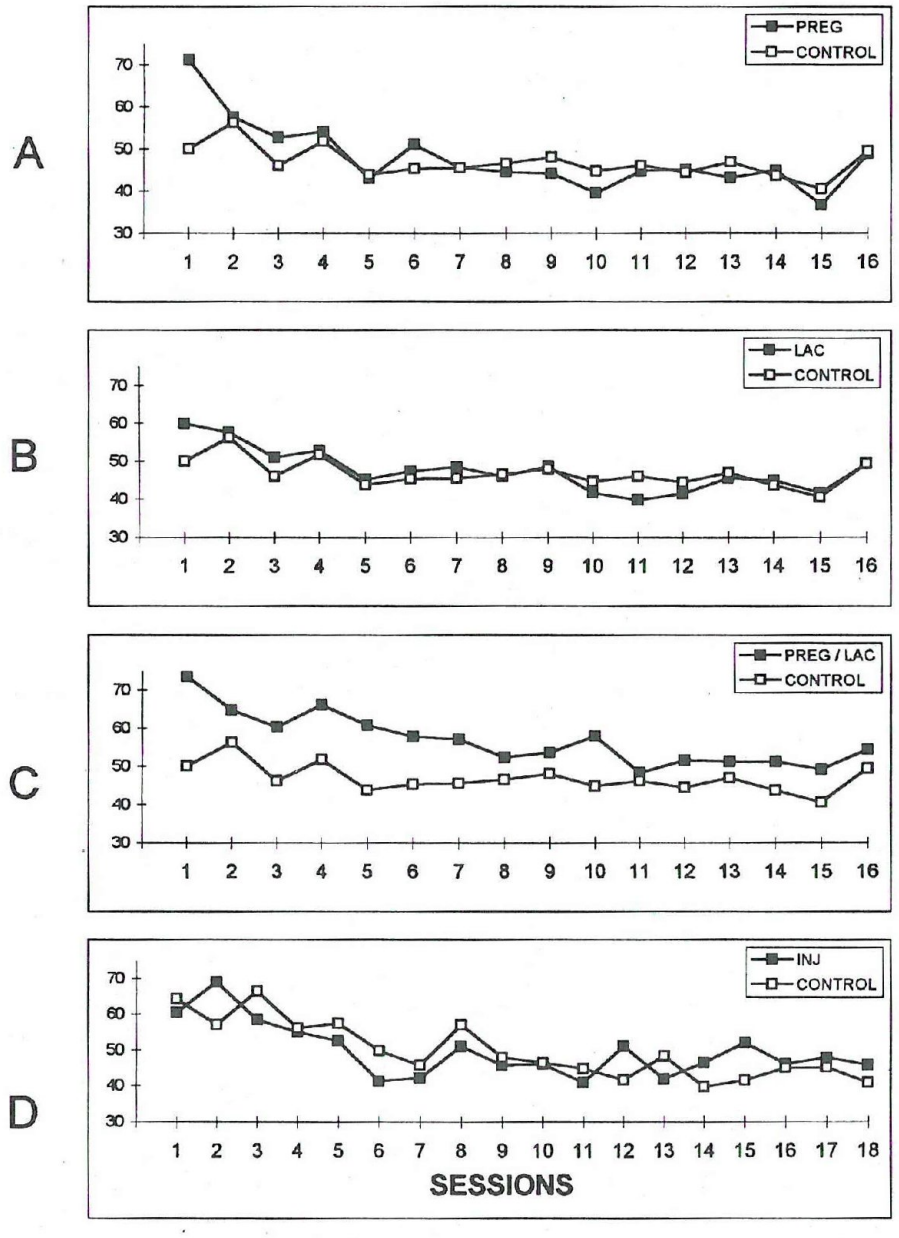


Figure 3. % Correct tray visits, mean ± SEM of five last sessions, for each test group and control group.

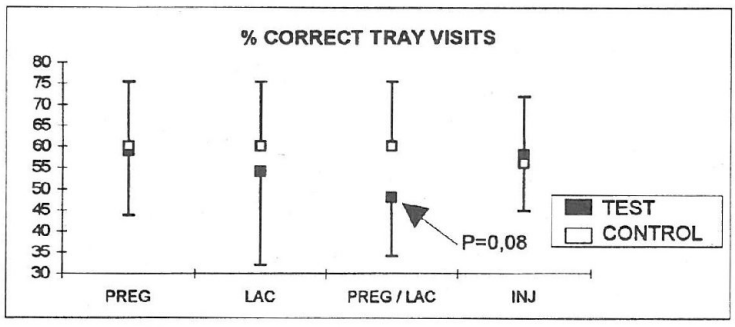


Table 2. Body weight and body weight gain of rat pups treated with daily ketamine injections 3 mg/kg from age of 4 to 18 days (inj) compared to pups injected with corresponding volumes of saline only using Student t-test (p=0.05). Mean weights ± standard error of the means are presented.

	Inj	Control
No. of pups	8	8
Weight day 4	8.8 ± 0.9	8.1 ± 0.6
Weight gain day 4 to 18	19.6 ± 1.0	20.1 ± 0.8
Weight day 35, start Skinner box	81 ± 3	81 ± 2
Weight day 105, end Skinner box	315 ± 11	324 ± 5

Figure 4. Total number of lever presses in each session for pups exposed to ketamine by direct injections (inj).

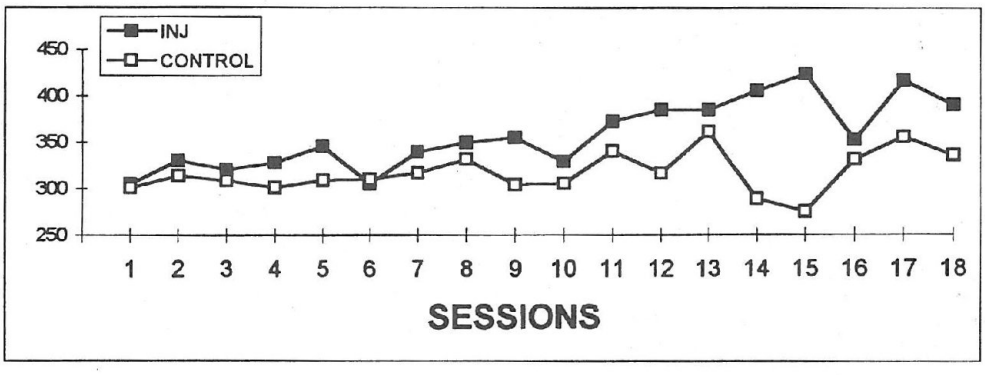
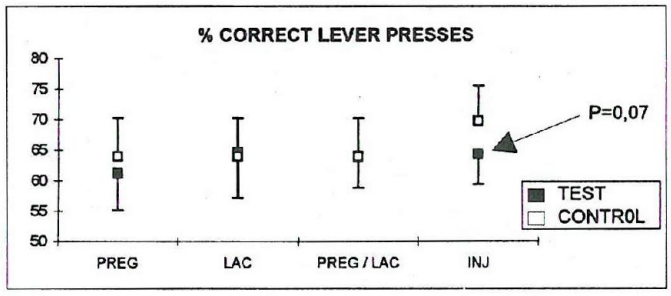


Figure 5. % Correct lever presses, mean ± SEM of five last sessions, for each test group and control group



statistically significant difference (p= 0.03) for the ketamine-injected group in Study 2.

Discussion

The mechanism by which ketamine produces behavioural effects has been investigated in several studies. There are indications that subanaesthetic doses of ketamine may impair prefrontal cortex function in rodents and produce symptoms in humans that indicate frontal lobe impairment by interacting with dopamine neurotransmission in this region. Verma and Moghaddam in 1996 utilised a spatial delayed alternation test to study the role of excitatory amino acids and dopamine receptors on associative functions of the prefrontal cortex in rats.

In a later study, the same scientists investigated the mechanism of ketamine on behaviour by conducting a dose-response study using microdialysis in conscious rats (*Moghaddam et al.* 1997). Their results indicated that low doses of ketamine (10-30 mg/kg) increased glutamatergic neurotransmission in the prefrontal cortex, and at 30 mg/kg ketamine also increased the release of dopamine in the prefrontal cortex.

The type of effects produced by ketamine may vary according to dose levels and most probably according to developmental stage of the exposed individual. In the present study, we administered ketamine at 2 repeated doses of 3 mg/kg, which was lower than the dose levels utilised by Moghaddam et al. (1997), who demonstrated increased glutamatergic neurotransmission and increased release of dopamine. However, developmental stages of fetal and perinatal life may represent higher sensitivity for behavioural impairment than stages later in life. The exposure to ketamine was indirect, repeated doses via the placenta during fetal life and via mother's milk, except for the pups exposed to ketamine by injections postnatally. The behavioural effects recorded in the present investigation may therefore well result from the same biochemical changes in the central nervous system as those recorded by Moghaddam et al. (1997). Our results recorded from the visual discrimination test program showed that decreased performance did not appear until the 10 % reinforcement schedule, which means the most demanding part of the program. This means that the observed learning impairment is only a weak one. The effects were most obvious for the perseveration error type and particularly in the pups that received ketamine injections (inj, Fig.1). In addition, the ketamine injected pups showed tendencies of increased activity and increased percentage of incorrect responses regarding lever presses (Figs. 4 and 5). The pups exposed during pregnancy and lactation (preg/lac) showed tendencies of increased activity and increased percentage of incorrect responses regarding tray visits (Figs. 2 and 3). A low percentage of correct responses could be secondary to a high activity level of rats rushing around without purpose. From our knowledge of ketamine effects, however, increased activity may more probably be a secondary effect of problems with learning the Skinner box tasks; increased

number of tray visits to look for water due to lack of knowledge on how to release the reinforcement, and increased number of lever presses due to lack of knowledge of a connection between the cue lamp and the correct lever to release the reinforcement. The most sensitive period for behavioural effects of ketamine turned out to be postnatally after direct injections into the pups.

In accordance with the results of Pallares et al. (1995) , who examined the immediate effects of ketamine after intraperitoneal administration on the acquisition of lever-press responses of adult male rats exposed to ketamine at 4-12 mg/kg in Skinner boxes, we can conclude that the decreased performance due to the increased perseveration type of error effect of the ketamine- exposed rat pups after indirect repeated dosing, could not be attributed to motor impairment, because the physical development of the ketamine-exposed rats was comparable to the control pups.

Summary

The first study was conducted with the administration of ketamine to rats during pregnancy, both pregnancy and lactation, or lactation, respectively, in order to localise the most sensitive period for behavioural effects of ketamine. In the second study, pups were injected subcutaneously with ketamine during the suckling period. No significant effects on litter size, physical signs, early movements and neuromuscular development of the pups were observed. From the discrimination behavioural tests in Skinner boxes differences between groups appeared at the most demanding tasks, the 10 % reinforcement schedule. In the first study, the behavioural activity as expressed by the total number of tray visits tended to be increased in the preg/lac group, although not statistically significant. For the animals exposed during lactation (lac) and especially those exposed during pregnancy and lactation (preg/lac), the percentage of correct tray visits tended to be decreased during the last 5 sessions.

In the second study, the total activity as expressed by total number of lever presses tended to be increased in the in pups exposed by postnatal injections (inj), although not statistically significant. In the same group the percentage of correct lever presses tended be decreased during the last 5 sessions. For the perseveration error type, there was a statistically significant increase in error number for the last 5 sessions in the injected (inj) group. Reduced learning ability was observed both for the pups that were indirectly exposed to ketamine both prenatally and during lactation, and for the pups receiving direct ketamine injections during the suckling period, more clearly however in the latter group.

Sammendrag

I den første undersøkelsen ble ketamine administrert til rotter henholdsvis under drektighet, under både drektighet og amming og under bare amming. Hensikten var å lokalisere den mest sensitive periode for adferdseffekter av ketamine. I den andre undersøkelsen ble rotteunger injisert ketamine subkutant i ammeperioden. Ingen signifikante effekter på kullstørrelse, fysiske tegn, tidlige bevegelser eller nevromuskulær utvikling ble observert. I diskriminasjonstestene i Skinner bokser ble forskjell mellom gruppene bare observert i det mest krevende programmet, som var 10 % forsterker nivå. I den første studien ble aktiviteten, uttrykt som totalt antall traubesøk, ikke statistisk signifikant økt i drektighet/amming- gruppen. For rottene i amming-gruppen, og spesielt i drektighet/amming-gruppen var det prosentvise antall korrekte traubesøk redusert for de 5 siste sesjonene. I den andre studien ble aktiviteten, uttrykt som totalt antall pedaltrykk, ikke statistisk signifikant økt hos rotteungene. Det prosentvise antall korrekte pedaltrykk var redusert for de 5 siste sesjonene. Antall feil av perseverasjonstypen var også statistisk signifikant økt for de 5 siste sesjonene i denne gruppen. Redusert læreevne ble observert både hos de rotteungene som ble indirekte eksponert for ketamine prenatalt og under amming, og hos de ungene som fikk direkte ketamine injeksjoner i ammeperioden, men læreevnen var mest redusert i den siste gruppen.

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