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SOME NEUROBEHAVIORAL EFFECTS OF KETAMINE IN CHICKS

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ABSTRACT

The neurobehavioral effects of ketamine (0.5 and 1 mg/kg, subcutaneously) were examined in 14 days-old domestic chicks using the open-field (5 minutes) and tonic immobility tests. Ketamine decreased locomotor activity as seen by a significant increase in the latency to move from the central square of the open-field arena and a decrease in the numbers of lines crossed (0.5 mg/kg, 30 and 60 minutes post-injection) in comparison with control values. Ketamine also decreased vocalization behavior. The depressed open-field activity was further supported by significant increases in the durations of tonic immobility of the ketamine-treated chicks in comparison with the control group. Xylazine challenge at 5 mg/kg, subcutaneously, two hours after the ketamine injections significantly increased the duration of sleep in both ketamine-treated groups by 59% and 100%, respectively in comparison with the control group. The data suggested that ketamine at subanesthetic doses reduces open-field activity in chicks, increases tonic immobility and increases the sedative action of xylazine.

بعض التأثيرات السلوكية العصبية للكتامين في أفراخ الدجاج

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الخلاصة

تم اجراء اختبارات الميدان المفتوح والسكون اللاحركي في أفراخ الدجاج بعمر 14 يوم بعد علاجها بالكتامين (0.5 و 1 ملغم/كغم، تحت الجلد). قلل الكتامين (0.5 ملغم/كغم، 30 و 60 دقيقة من الحقن) من النشاط الحركي للأفراخ والذي لوحظ بشكل زيادة في الوقت اللازم للحركة من المربع المركزي في الميدان المفتوح وانخفاض في عدد الخطوط المقطوعة مقارنة مع مجموعة السيطرة. وقلل الكتامين من سلوك الصياح. وقد تم دعم الأنخفاض الحاصل في النشاط الحركي داخل الميدان المفتوح بزيادة معنوية في فترة السكون اللاحركي في الأفراخ المعاملة بالكتامين مقارنة مع مجموعة السيطرة. أدى التحدي الدوائي بالزايلازين (5 ملغم/كغم، تحت الجلد) بعد ساعتين من العلاج بالكتامين الى زيادة في فترة النوم في الفراخ المعاملة و بنسبة 59% و100% ، على التوالي مقارنة مع مجموعة السيطرة. تشير البيانات الى ان الكتامين بجرع غير مخدرة يقلل من النشاط الحركي داخل الميدان المفتوح مع زيادة في فترة السكون اللاحركي في الأفراخ فضلاً عن الزيادة في الفعل المسكر للزايلازين.

INTRODUCTION

Ketamine is an N-methyl-D-aspartate receptor antagonist used in man (1) and animals (2,3) as a general anesthetic agent usually in combination with sedative analgesics. Recent reports indicate that the central nervous system actions of ketamine at subanesthetic doses are different from its overt sedative or depressant ones (4-6). Ketamine was reported to induce cognitive dysfunctions in man affecting motor adjustments (7), producing positive mood effects (8) and might mimic the memory impairment associated with acute, but not chronic, forms of schizophrenia (9). In laboratory animals, ketamine induces a variety of behavioral effects and might cause neurotoxicosis eventually (10,11). Ketamine induces behavioral and regional brain metabolic activation in mice (12), causes yawning in rats (13), reverses catalepsy by haloperidol in rats (14), affects tunnel maze and water maze performance in rats (15) and increases locomotor activity in mice (16) and rats (17). Ketamine mixture with the alpha2 agonist xylazine causes filial imprinting in chicks on day 8 of age (18). Ketamine also possesses anticonvulsant activity in mice (19) and chicks (20).

Although the anesthetic effect of ketamine is well understood in chickens, its neurobehavioral effects in this species are not fully known. The open-field paradigm has been used to characterize the behavioral performance of chicks, as young chick model is suitable for biomedical researches especially those related to effects of drugs or toxicants (21-23). Using this animal model, the behavioral performance of 14-days old chicks were examined under the influence of subanesthetic doses of ketamine. Interests are increasing on the effects of subanesthetic doses of ketamine as this drug can be abused (24).

MATERIALS AND METHODS

Unsexed, 14 days old, domestic broiler chicks were housed under standard poultry housing conditions with water and feed given ad libitum. The chicks were treated subcutaneously (s.c.) with physiological saline solution at 5 ml/kg body weight (control group) or with ketamine HCl (Ketalar, Parke-Davis, U.K.) at 0.5 and 1 mg/kg body weight. Ketamine injectable solution was prepared in physiological saline solution, and the volume of administration was at 5 ml/kg body weight. The choice of ketamine doses was based on preliminary experiments in chicks in which anesthetic doses (3,25) were avoided and they did not produce overt signs of sedation in the chicks such as bowing of the head, closed eyelids, immotility, decreased distress calls or recumbency (21,26). After the injection of ketamine the chicks were monitored for the open field activity (21-23) and the tonic immobility performance (27).

The chicks were subjected to open-field activity test 30 and 60 minutes after the ketamine injection. . Each chick was placed alone on the center of the arena of an open field box (90x60x50 cm); the arena was divided into 24 equal squares and 50 g of wheat grains were scattered on the surface (21). In the open-field test the following behavioral patterns were measured by two experimenters as described earlier (21-23) with some modifications:

1. Latency to move from the center square.
2. Number of lines crossed by both feet (ambulation).
3. Number of escape jumps.
4. Frequency of defecations
5. Scoring of distress calls (vocalization):

1, 1-2 calls
2, 3-4 calls
3, > 5 calls

6. Scoring of pecking behavior

0, no pecking
1, 1-2 times
2, 3-4 times
3, > 5 times

After the open-field activity test, each chick was subjected to tonic immobility test (27) by holding the chick in both hands and placing it on a wooden table for 15 seconds, the hands were then withdrawn and the chick was timed to upright itself and standing. Two hours after the administration of ketamine, the chicks were challenged with a sedative dose (5 mg/kg, s.c.) (2,25) of xylazine (2% solution, Sanofi Sante Nutrition Animale, France). Xylazine was diluted with physiological saline solution and the volume of administration was at 5 ml/kg body weight, s.c. The latency to onset of sleep (loss of righting reflex after placing the chick on one side) and duration of sleep were recorded.

All the experiments complied with regulations addressing animal use, and proper attention has been given to ethical consideration towards the chicks used in the present study. Continuous data were statistically analyzed by one way analysis of variance followed by the least significant difference test (28). Non-parametric data were subjected to Mann-Whitney-U-test (29). The level of significance was at $P< 0.05$.

RESULTS

The 5-minutes open-field activity patterns and tonic immobility performance of chicks treated with ketamine at 0.5 and 1 mg/kg, s.c. are shown in table 1. In general, ketamine decreased the locomotor activity as seen by a significant increase in the latency to move from the central square of the open-field arena and a decrease in the numbers of lines crossed (0.5 mg/kg, 30 and 60 minutes post-injection) in comparison with control values. Ketamine-induced hypoactivity in the chicks was best manifested by ambulation and vocalization behaviors (Table 2). This effect was further supported by significant increases in the durations of tonic immobility of the ketamine treated chicks in comparison with the control group (Table 1).

The xylazine challenge at 5 mg/kg, s.c. two hours after ketamine injections significantly increased the durations of sleep in both ketamine-treated groups by 59% and 100%, respectively in comparison with the control group (Table 2).

DISCUSSION

Ketamine is a well known anesthetic in veterinary practice usually used with sedative analgesics such as xylazine (2,3,25). The doses of ketamine used in the present study were neither anesthetic nor overtly sedative in the chicks (2,3,25). The higher dose of ketamine (1 mg/kg) used in the present study was much less than the median effective (14mg/kg, intravenously) and median lethal (67.9 mg/kg, intravenously) doses of this drug in chickens (3). In spite of the low doses of ketamine, the behavioral paradigms used in the present study detected a depressant action of

Table 1. Effects of ketamine on 5-minutes open-field activity and tonic immobility test in chicks

Variable	Ketamine (mg/kg, subcutaneously)					
	0 (saline-control)		0.5		1.0	
	0.5 h	1 h	0.5 h	1 h	0.5 h	1 h
Latency to move (seconds)	5±2	5±2	20±4*	213±69*	73±56	87±53[a]
Lines crossed	32±16	30±13	9±6*	1±1*	20±8	18±10
Escape jumps	7±5	5±3	1±1	1±1	4±3	2±1
Distress calls (scores)	3.0±0	3.0±0	2.5±0.5	0.3±0.3*	1.0±0.7*	0.8±0.8*
Pecking (scores)	0.5±0.3	0.3±0.3	0.3±0.3	1.8±0.6	2.3±0.5	1.3±0.8
Defecations	2.3±1.0	1.0±0	1.0±0	0±0	0.5±0.3	0.3±0.3
Tonic immobility (seconds)	21±6	19±5	61±10*	57±9*	83±26*	65±20*

*Significantly different from the respective control value, $P< 0.05$.
[a] Significantly different from the 0.5 mg/kg dose group of ketamine, $P< 0.05$.
N=8 chicks/group.

Table 2. Xylazine (5 mg/kg, subcutaneously)-induced sleep (loss of righting reflex) in chicks treated two hours earlier with ketamine

Ketamine (mg/kg, subcutaneously)	Latency to onset of sleep (minutes)	Duration of sleep (minutes)
0 (saline-control)	53±8	17±1
0.5	46±14	27±4*
1.0	48±27	34±5*

*Significantly different from the respective control value, $P< 0.05$.
N=8 chick/group.

ketamine in the chicks. Furthermore, xylazine challenge two hours after the ketamine administration revealed the supposedly subtle and residual depressant effects of ketamine in the chicks. The latter finding suggests that xylazine not only potentiates the anesthetic action of ketamine (2) but also increases its residual depressant effects.

The sets of open-field activity and tonic immobility tests present novel tasks and challenging environment for the bird to cope with (17,21-23,30). In addition CNS depressants are known to decrease ambulation and related activities in chicks and rodents in the open-fields test, whereas stimulants might increase them (21-23,30,31). The present findings correlate with the reported selective depressant effects of ketamine against chemical-induced convulsion in chicks (20). Further, ketamine did not disrupt spontaneous locomotor movement in rats (5). Similarly, in the present study, the spontaneous movements were not completely abolished in chicks treated with ketamine. However, in contrast to the present findings, ketamine was reported to increase locomotor activity in mice (16) and rats (17). This discrepancy could be attributed to the differences in animal species, dose of ketamine and the behavioral paradigm used. Limited reports are available on the behavioral effects of ketamine in chickens (3,18,20). The present findings further add to and extend the behavioral characteristics of subanesthetic doses of ketamine in the chicks.

In conclusion, ketamine-induced depression at subanesthetic doses in chicks was characterized by the decrease in the open field activity and increase in tonic immobility as well as increase in the sedative action of xylazine.

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