啓明醫大論文集 第 11 卷 第 1 號
The Keimyung Univ Med J
Vol 11, No. 1, March, 1992

A Study on the Ketamine-induced Analgesia and Locomotor Activity in Mice

Department of Pharmacology, School of Medicine, Keimyung University, Taegu

Soo Kyung Kim, MD; Seong Ryong Lee, MD

Introduction

The previous study[1], in our laboratory, has demonstrated that the concentrations of norepinephrine(NE) and dopamine(DA) were decreased by ketamine and morphine administration in mouse brain. Many studies have suggested that ketamine[2-4], like morphine[5-7], interferes with the monoamine metabolism and increases the rate of its turnover in the striatum.

Ketamine, a dissociative anesthetic agent, is known to induce post-anesthetic mood change, confusion and irrational behavior in some humans. In rat, ketamine produced dose-related analgesia, stimulation of locomotor activity and stereotyped behavior[8-11]. Also, it was observed that analgesia produced by ketamine was antagonized by naloxone[12-14]. Thereafter, the antagonism of ketamine-induced analgesia by naloxone has been confirmed by De Simoni et al[15,16]. But the relationship between ketamine and opioid receptor on the cataleptic response have been conflicted yet[17]. The tolerance to cataleptic behavior response of ketamine[18,19] and cross-tolerance with morphine has been reported. Also, the brain dopaminergic system has been accepted as important substance which causes stereotyped behavior and change of motor activity in animal[20].

In our attempt, we were to study whether naloxone and the presumptive changes of the catecholamine level induced by several drugs(apomorphine, haloperidol, reserpine and α-methyl-p-tyrosine) determine influences on the analgesic effect and locomotor activity by ketamine administration. And, the relationship between ketamine and opioid antagonist or presumptive changes of the analgesic action and motor activity by agents that can alter the concentration of catecholamine were investigated.

Materials and Methods

Animals used for this study were ICR mice weighing 25−30g of either sex. The animals were housed under standardized conditions for 3 weeks before the test they allowed. The food and water were given ad libitum. The mice were divided into 7 groups. The experimental groups are followings.

(a) Control groups: Saline, naloxone, apomorphine, haloperidol, reserpine, or α-methyl-p-tyrosine (α-MPT) was alone injected.

(b) Ketamine groups: 20, 40, 60, or 80mg/kg of ketamine was injected.

(c) Naloxone pretreatment group: 5mg/kg of naloxone was injected to 20mg/kg and 80mg/kg of ketamine group.

(d) Apomorphine pretreatment group: 400μg/kg of apomorphine was injected to 20mg/kg and 80mg/kg of ketamine group.

(e) Haloperidol pretreatment group: 200μg/kg of haloperidol was injected to 20mg/kg and 80mg/kg of ketamine group.

(f) Reserpine pretreatment group: 5mg/kg of reserpine was injected to 20mg/kg and 80mg/kg of ketamine group.

(g) α-MPT pretreatment group: 250mg/kg of α-MPT was injected to 20mg/kg and 80mg/kg of ketamine group.

Analgesia was assessed by the modified tail-flick method as previous described[21] in immediately, 30,

60, 90, and 120 minutes after intraperitoneal injection of each drug. The reaction time for basal condition was controlled to be 2-3 seconds. The flick response was recorded through an electronic stopwatch.

All behavioral tests were carried out between 9 A.M. and 12 A.M. in a dim illuminated room maintained at a temperature of 20±2°C. Immediately, 30, 60, 90, and 120 minutes after intraperitoneal injection of each drug, mice were examined in perspective boxes(42cm×42cm×32cm). The activity was assessed by counting the numbers of interruptions of the invisible infrared light beam occuring in each 5 minutes period. Then, the numbers of activity were checked by animal activity monitoring system that was purchased from Omnitech electronics, In.(Columbus, Ohio 43228) and interpretated by computerized analyzer. The parameters of behavior change test in this study were locomotor activity and stereotyped behavior.

The drugs used in these experiment were ketamine(Yuhan Co.), naloxone(Sigma Chemical Co.), apomorphine(Sigma Chemical Co.), haloperidol(Sigma Chemical Co.), reserpine(Sigma Chemical Co.), and α-MPT(Sigma Chemical Co.). All drugs were administrated intraperitoneally and all solution of drugs were given in volumes of 10ml/kg.

The data obtained were expressed as the mean ±S.E. The means of the responses recorded at each time were compared with each control group using Student's t-test, and $p<0.05$ was taken as the level of significance.

Results

Effects on analgesic action

Ketamine caused a dose-dependent increase in tail-flick latency(TFL) above control value. Especially, administration of ketamine (80mg/kg) caused a significant increase of analgesic action(Table 1, Fig 1). Naloxone alone did not affect an analgesic action, but apomorphine, haloperidol, reserpine, or α-MPT caused a moderate increase of analgesic action(Table 1). The ketamine(20mg/kg)-induced analgesic action was not affected significantly by above drugs. But naloxone and reserpine inhibited the increase of ketamine(20mg/kg)-induced analgesic action slightly. Haloperidol, apomorphine, and α-MPT potentiated the increase of ketamine(20 mg/kg)-induced analgesic action slightly(Table 2). The ketamine(80mg/kg)-induced analgesic action was inhibited significantly by naloxone or haloperidol and slightly by apomorphine. Reserpine and α-MPT administration did not affect the increase of ketamine-induced analgesic action(Table 3).

Table 1. Effects of ketamine, naloxone, apomorphine, haloperidol, reserpine, and α-MPT on the analgesic action

Treatment \ Time(min.)		0	30	60	90	120
Control(saline)		2.20±0.13	2.23±0.12	2.19±0.20	2.12±0.10	2.00±0.13
Ketamine	(20mg/kg)	2.20±0.20	2.60±0.15	2.55±0.45	2.67±0.24	2.63±0.11*
	(40mg/kg)	2.40±0.35	2.50±0.18	2.27±0.18	3.03±0.39*	2.68±0.34
	(60mg/kg)	2.08±0.16	2.93±0.57	2.48±0.17	3.15±0.15**	3.05±0.30**
	(80mg/kg)	3.32±0.91	3.48±0.29**	3.98±0.49**	3.60±0.65*	4.00±0.35**
Naloxone	(5mg/kg)	2.00±0.12	2.16±0.20	2.20±0.60	2.01±0.18	2.08±0.24
Apomorphine	(400μg/kg)	2.78±0.33	2.73±0.12	3.38±0.58	2.75±0.19*	2.68±0.23*
Haloperidol	(200μg/kg)	2.90±0.16*	2.62±0.36	2.60±0.11	2.46±0.14	2.84±0.02**
Reserpine	(5mg/kg)	2.40±0.10	2.50±0.30	2.55±0.15	2.40±0.10	2.40±0.10*
α-MPT	(250mg/kg)	2.81±0.27	2.58±0.20	2.76±0.20	2.82±0.27*	2.83±0.23**

Data are expressed as Mean ±S.E.
* : $p<0.05$, ** : $p<0.01$
α-MPT : α-methyl-p-tyrosine

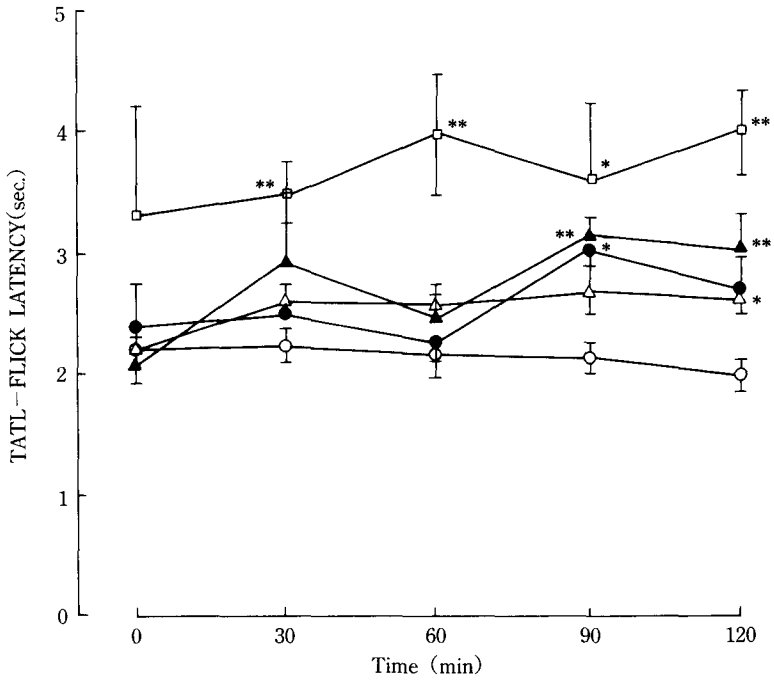

Fig 1. Changes of tail-flick latency by ketamine administration.

○—○ : Control, △—△ : Ketamine 20mg/kg.
●—● : Ketamine 40mg/kg, ▲—▲ : Ketamine 60mg/kg.
□—□ : Ketamine 80mg/kg, * : $p<0.05$, ** : $p<0.01$

Table 2. Effects of naloxone, apomorphine, haloperidol, reserpine, and α-MPT on the ketamine (20mg/kg)-induced analgesic action

Pretreatment \ Time(min.)	0	30	60	90	120
Control (ketamine)	2.20±0.20	2.60±0.15	2.55±0.45	2.67±0.24	2.63±0.11
Naloxone	2.57±0.25	2.42±0.27	2.49±0.09	2.50±0.66	2.30±0.27
Apomorphine	2.62±0.39	4.03±1.11	3.28±0.15	3.25±0.55	2.85±0.50
Haloperidol	2.90±0.40	3.28±0.29	2.77±0.27	2.85±0.17	3.15±0.22
Reserpine	2.33±0.43	2.53±0.40	2.40±0.32	2.40±0.49	2.30±0.52
α-MPT	4.27±1.21	3.07±1.34	3.43±0.56	3.50±0.12**	2.40±0.22

** : $p<0.01$

Table 3. Effects of naloxone, apomorphine, haloperidol, reserpine, and α-MPT on the ketamine (80mg/kg)-induced analgesic action

Pretreatment \ Time(min.)	0	30	60	90	120
Control (ketamine)	3.32±0.91	3.48±0.29	3.98±0.49	3.60±0.65	4.00±0.35
Naloxone	3.76±0.40	2.88±0.45	2.44±0.15*	2.90±0.10	3.23±0.13
Apomorphine	3.23±0.51	4.45±1.76	3.38±0.13	2.60±0.09	2.63±0.18**
Haloperidol	2.84±0.15	2.88±0.21	2.65±0.19*	2.80±0.15	2.86±0.22*
Reserpine	3.60±0.40	3.60±0.40	3.70±0.10	3.52±0.45	3.20±0.21
α-MPT	2.75±0.86	2.53±0.73	2.46±0.21	2.30±0.12	3.04±0.47

* : $p<0.05$, ** : $p<0.01$

Effects on locomotor activity

Ketamine alone(20mg/kg and 40mg/kg) produced time-related variety effects that exhibited increase of locomotor activity at early time after injection (<60minute) and decrease of it at late time after injection(120 minute). But, administration of ketamine (80mg/kg) showed increase of locomotor activity(Table 4, Fig 2). Naloxone or apomorphine exhibited a moderate increase of locomotor activity. α-MPT exhibited a decrease of locomotor activity significantly(Table 4). The change of ketamine(20 mg/kg)-induced locomotor activity was not inhibited by naloxone, but inhibited only by α-MPT(Table 5). The increase of ketamine(80mg/kg)-induced locomotor activity was not affected by naloxone, but inhibited by apomorphine, haloperidol, reserpine, and α-MPT significantly(Table 6).

Effetcs on stereotyped behavior

The ketamine-induced stereotyped behavior exhibited similar to the change of locomotor activity. At early time after ketamine (20mg/kg and 40mg/kg) injection(<60minute), stereotyped behavior showed a increase, but at late time, showed a decrease significantly. In high does (80mg/kg) of ketamine, stereotyped behavior did not show significant different changes(Table 7, Fig 3). Ketamine (20mg/kg)-induced stereotyped behavior was not affected by above drugs except haloperidol and α-MPT (Table 8). The ketamine(80mg/kg)-induced stereotyped behavior was not affected by naloxone or α-MPT and moderately inhibited by apomorphine and significantly inhibited by reserpine and significantly increased by haloperidol(Table 9).

Discussions

Recent reports have suggested that the analgesic action and locomotor stimulant action of ketamine could be mediated by opioid receptor[12-14]. However, other evidences indicate that ketamine has negligible affinity for specific opioid receptors and not antagonized by naloxone using detection ketamine binding to opioid receptor[10,17,22,23]

In light of these conflicting finding, the purpose of the present study was to reexamine the analgesic action and locomotor stimulant effects of ketamine and to determine whether such actions are influenced by the opioid antagonist, naloxone, or monoaminergic system.

This study has confirmed the previous finding[8-11] that subanesthetic doses of ketamine produces analgesia and excitatory effects including regular and highly stereotypic locomotor phenomenon in unlesioned rats. To examine the effects of various doses of ketamine, at five different times after injection, a dose/time-dependent analgesic effect and behavioral change have been estabilished. In this study, ketamine produced a dose-dependent analgesia, and naloxone or haloperidol partially inhibited the analgesic effect of ketamine (80mg/kg). The pretreatment of apomorphine produced a decrease of analgesic effect of ketamine (80mg/kg) slightly. Reserpine, haloperidol, and α-MPT did not significantly affect the change of tail-flick latency(TFL) induced by ketamine.

Many studies have suggested a possible relationship between analgesia and brain catecholamine metabolism. There are also confliciting on the importances of different monoaminergic systems in the spinal cord[24], brain stem[25], and forebrain[26,27] as well as in the injuried tissue[28]. The pain induced by thermal stimulation is strongly modulated by mu receptor agonist[29,30] in brain stem and spinal cord through the serotonergic receptor in spinal cord[25]. A a preliminary study[1] in our laboratory demonstrated that ketamine caused decrease of brain NE and DA concentration, especially DA concentration in mice. Also, there were a few conflicted studies that the ketamine-induced analgesia was produced by opioid receptor.

It has been noted by many authers that the open field behavior is very complex and not representative of many particular domains of behavior. But, it is true that brain dopamine systems play an important role in open-field locomotor activity and exploratory behavior[20]. Therefore, we were to explain in some detail how dopaminergic system may affect explo-

Table 4. Effects of ketamine, naloxone, apomorphine, haloperidol, reserpine, and α-MPT on the locomotor activity

Treatment \ Time (min.)		0	30	60	90	120
Control (saline)		31.41±2.59	30.20±3.00	28.90±5.00	30.00±2.02	27.60±0.93
Ketamine	(20mg/kg)	44.00±4.39*	45.29±7.55	22.60±4.93	15.67±4.48**	11.25±6.21*
	(40mg/kg)	55.67±6.02**	52.55±4.05**	38.50±8.86	14.33±9.87**	12.00±5.78*
	(60mg/kg)	56.75±6.98**	49.00±6.29	54.50±10.47*	39.00±9.29	21.33±7.42
	(80mg/kg)	55.50±7.86*	59.00±7.93*	60.75±9.28*	56.67±8.09**	55.00±2.89**
Naloxone	(5mg/kg)	40.00±3.29	35.00±2.60	42.00±6.60	42.30±3.26**	41.60±7.20
Apomorphine	(400μg/kg)	46.50±5.00*	49.25±15.27	26.50±4.44	35.75±6.43	21.25±1.97
Haloperidol	(200μg/kg)	42.17±6.14	36.83±4.85	23.50±7.50	25.83±8.72	18.83±7.51
Reserpine	(5mg/kg)	44.80±12.68	32.40±12.27	39.67±8.36	32.80±2.08	21.40±0.93
α-MPT	(250mg/kg)	27.50±3.82	27.70±5.05	28.10±6.82	13.10±2.87**	9.40±1.86**

* : $p<0.05$, ** : $p<0.01$

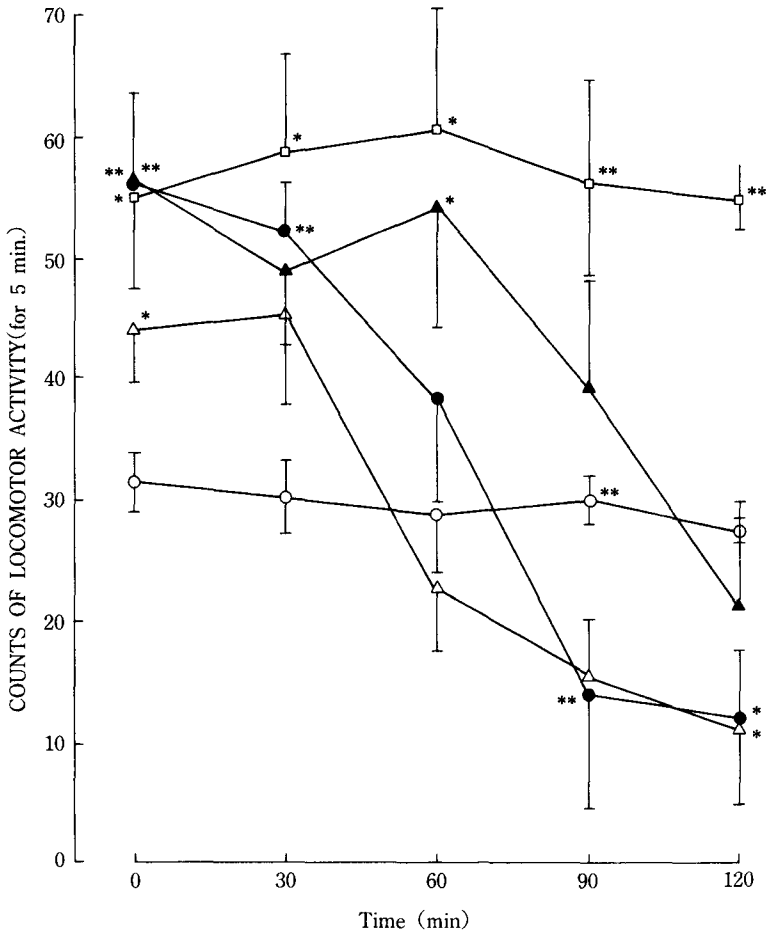

Fig 2. Changes of tail-flick latency by ketamine administration.

○—○ : Control, △—△ : Ketamine 20mg/kg.
●—● : Ketamine 40mg/kg, ▲—▲ : Ketamine 60mg/kg.
□—□ : Ketamine 80mg/kg, * : $p<0.05$, ** : $p<0.01$

ratory behavior. It is important to emphasize that many different classes of drugs may influence exploratory behavior. Apomorphine, haloperidol, reserpine, and α-MPT as those drugs were employed in this study. The overactivation of DA receptor by apomorphine with direct agonist caused slight increase of locomotor activity and changelessness of stereotyped behavior in treated group of ketamine 80mg/kg. But, the changelessness or decrease of stereotyped behavior supported by the observation that apomorphine blocks latent learning[31]

The effect of monoamine depletion with reserpine produced decrease of locomotor activity and stereotyped behavior by ketamine significantly. The

Table 5. Effects of naloxone, apomorphine, haloperidol, reserpine, and α–MPT on the ketamine (20mg/kg)-induced locomotor activity

Pretreatment \ Time(min.)	0	30	60	90	120
Control (ketamine)	44.00±4.39	45.29±7.55	22.60±4.93	15.67±4.48	11.25±6.21
Naloxone	43.50±12.62	45.75±7.12	34.00±11.23	18.33±11.39	12.33±7.84
Apomorphine	44.50±11.31	38.17±11.53	23.33±5.16	15.50±4.07	13.83±3.22
Haloperidol	29.50±10.65	24.00±2.27*	22.25±3.42	16.50±1.55	15.00±3.03
Reserpine	51.00±13.44	39.75±11.22**	33.50±6.06	25.00±8.41	5.75±2.50
α-MPT	52.00±8.02	14.50±3.93**	11.75±4.94	8.75±3.45	13,50±5.61

*: $p<0.05$, **: $p<0.01$

Table 6. Effects of naloxone, apomorphine, haloperidol, reserpine, and α-MPT on the ketamine (80mg/kg)-induced locomotor activity

Pretreatment \ Time(min.)	0	30	60	90	120
Control (ketamine)	55.50±7 86	59.00±7.93	60.75±9.28	56.67±8.09	55.50±5.89
Naloxone	49.83±7.16	41.00±6.13	42.17±5.38	45.00±8.54	44.00±11.22
Apomorphine	36.25±9.70	38.50±13.17	35.00±4.88*	41.25±14.34	32.25±8.35**
Haloperidol	26.67±6.27	22.33±5.26**	29.00±6.30*	54.67±10.19	46.33±7.59
Reserpine	32.00±0.80	24.00±0.10**	23.50±2.36**	13.50±1.50**	1.25±0.21**
α-MPT	37.30±12.19	28.00±7.22*	32.50±12.80	32.25±4.89*	24.75±6.17**

*: $p<0.05$, **: $p<0.01$

Table 7. Effects of ketamine, naloxone, apomorphine, haloperidol, reserpine, and α-MPT on the stereotyped behavior

Treatment \ Time (min.)		0	30	60	90	120
Control		34.20±0.20	36.70±2.90	31.20±4.20	36.00±2.70	33.00±5.60
Ketamine	(20mg/kg)	48.00±1.55**	33.67±4.70	27.17±4.80	16.00±2.08**	15.75±4.94**
	(40mg/kg)	42.17±3.53*	42.50±6.59	25.67±5.14	15.00±5.51**	7.50±0.63**
	(60mg/kg)	31.17±7.05	39.50±6.16	28.83±4.85	26.33±4.10	31.25±7.78
	(80mg/kg)	39.83±5.39	33.83±9.54	31.50±8.19	33.00±2.08	22.00±10.00
Naloxone	(5mg/kg)	30.60±6.20	32.00±5.90	36.20±8.20	28.42±3.20	27.80±5.60
Apomorphine	(400μg/kg)	32.25±3.45	37.25±9.94	23.50±2.10	22.75±0.85**	21.50±1.55
Haloperidol	(200μg/kg)	34.83±2.44	25.33±2.72*	25.17±4.95	21.33±0.37*	18.33±2.80**
Reserpine	(5mg/kg)	30.20±4.98	28.20±8.34	18.60±6.62	10.80±5.98**	3.00±0.10**
α-MPT	(250mg/kg)	26.40±3.00	32.63±2.00	27.30±2.85	21.90±2.58**	22.30±2.25

*: $p<0.05$, **: $p<0.01$

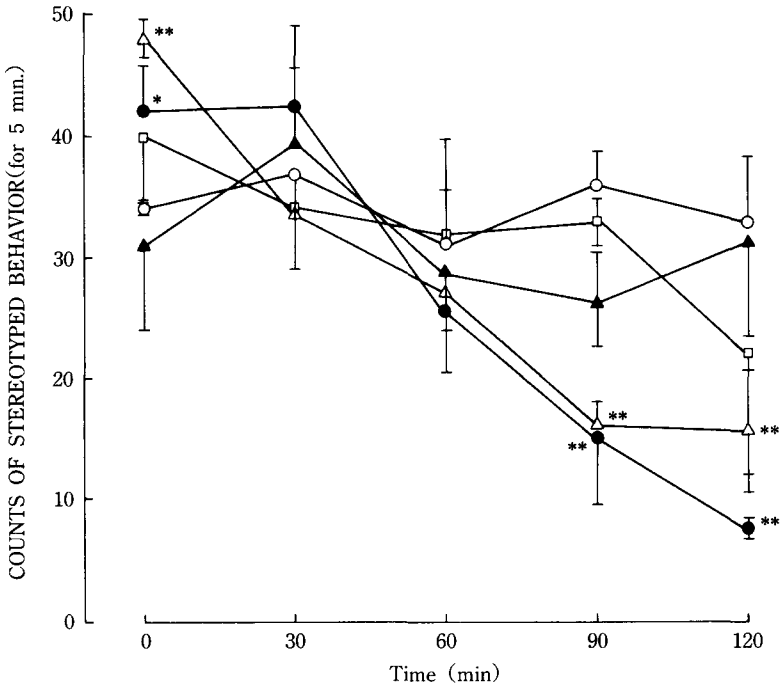

Fig 3. Changes of tail-flick latency by ketamine administration.

○—○ : Control, △—△ : Ketamine 20mg/kg.
●—● : Ketamine 40mg/kg, ▲—▲ : Ketamine 60mg/kg.
□—□ : Ketamine 80mg/kg, * : $p<0.05$, ** : $p<0.01$.

Table 8. Effects of naloxone, apomorphine, haloperidol, reserpine, and α-MPT on the ketamine (20mg/kg)-induced stereotyped behavior

Pretreatment \ Time(min.)	0	30	60	90	120
Control (ketamine)	48.00±1.55	33.67±4.70	27.17±4.80	16.50±2.08	15.75±4.94
Naloxone	45.00±5.24	34.40±4.45	24.00±4.73	15.00±9.54	11.67±5.36
Apomorphine	37.50±5.25	36.50±6.56	26.83±3.35	21.50±3.01	24.83±5.68
Haloperidol	42.25±6.09	30.50±2.84	29.25±3.07	19.75±3.84	28.50±2.75*
Reserpine	31.75±7.52	29.75±4.15	30.50±1.50	20.75±6.80	9.00±4.14
α-MPT	24.00±6.76**	24.50±6.49	14.00±4.69	16.50±2.25	19.00±2.27

* : $p<0.05$, ** : $p<0.01$

Table 9. Effects of naloxone, apomorphine, haloperidol, reserpine and α-MPT on the ketamine (80mg/kg)-induced stereotyped behavior

Pretreatment \ Time(min.)	0	30	60	90	120
Control (ketamine)	39.83±5.39	33.83±9,54	31.50±8.19	33.00±2.08	22.00±10.00
Naloxone	37.80±7.36	42.75±2.81	40.40±5.06	40.33±9.70	32.65±4.80
Apomorphine	25.00±10.52	32.75±7.33	19.75±6.26	27.25±9.57	14.25±3.97
Haloperidol	29.00±6.30	40.50±1.80	42.75±5.59	48.17±1.96	46.00±3.80*
Reserpine	31.67±10.84	17.50±4.63	16.25±0.78	8.50±4.84**	13.50±1.90
α-MPT	31.25±9.58	35.50±5.87	38.00±5.02	26.25±4.13	24.75±5.11

* : $p<0.05$, ** : $p<0.01$

effect of dopamine antagonist, haloperidol, and α-MPT produced moderate changes of locomotor activity and stereotyped behavior. Naloxone did not affect the behavioral change of ketamine.

The results obtained from this study, suggest that analgesic action of ketamine may be due to opioid receptor and its locomotor activity is influenced by brain monoaminergic system rather than opioid receptor. But, we did not obtain significant results on the ketamine-induced stereotyped behavior.

Summary

In this study, we were to examine the analgesic action and changes of motor activity by ketamine and its mechanisms. Ketamine caused the dose dependent increase of analgesic action and locomotor activity, but did not exhibit significant effect on stereotyped behavior. Naloxone inhibited the increase of ketamine-induced analgesic action, but did not inhibit increase of locomotor activity. Apomorphine and haloperidol inhibited the increase of ketamine-induced analgesic action and locomotor activity. Reserpine and α-MPT did not affect ketamine-induced analgesia, but inhibited increase of ketamine-induced locomotor activity.

The results of this study suggest evidence that analgesia of ketamine may be due to opioid receptor and its locomotor activity is influenced by brain monoaminergic system rather than opioid receptor. We did not obtain significant results on the ketamine-induced stereotyped behavior.

References

1. Kim SK: Effects of ketamine and morphine on the changes of brain catecholamine concentration in mice. *Keimyung Univ Med J* 1990; 9(1): 61-70.
2. Hatch RC, Ruch T: Experiments on antagonism of ketamine anesthesia in cats given adrenergic stimulants alone and in combination. *Ame J Vet Res* 1974; 35: 35-39.
3. Glisson SN, El-Etr AA, Bloor BC: The effect of ketamine upon norepinephrine and dopamine levels in rabbit brain parts. *Naunyn Schmiedbergs Arch Pharmacol* 1976; 295: 149-152.
4. Ylitalo P, Saarnivaara L, Ahtes L: Effect of ketamine anesthesia on the content of monoamines and their metabolites in the rat's brain. *Acta Anesth Scand* 1976; 20: 216-220.
5. Kuchinsky K, Hornykiewicz O: Morphine catalepsy in the cat; relation to striatal dopamine metabolism. *Eur J Pharmacol* 1972; 19: 119-122.
6. Korf J, Bunney BS, Aghajanian GK: Noradrenergic neurons: morphine inhibition of spontaneous activity. *Eur J Pharmacol* 1974; 25: 165-169.
7. Paalzow G, Paalzow L: Morphine-induced inhibition of different pain responses in relation to turnover of rat's brain noradrenaline and dopamine. *Psychopharmacologia*(Berl.) 1975; 45: 9-20.
8. Lakin ML, Winters WD: Behavioral correlates of naloxone inhibition of analgesia induced by various CNS excitatory drugs in the rat. *Proc West Pharmacol Soc* 1978; 21: 27-30.
9. Myslobodsky M, Ackermann RF, Mansour R, et al: Ketamine-induced rotation and its interaction with naloxone in rats. *Brain Res* 1979; 172: 191-195.
10. Smith DJ, Perrotti JM, Mansell Al, et al: Ketamine analgesia is not related to an opiate action in the periaqueductal gray region of the rat brain. *Pain* 1985; 21: 253-265.
11. Winters WD, Hance AJ, Cadd GC, et al: Seasonal and sex influences on ketamine-induced analgesia and catalepsy in the rat; a possible role for melatonin. *Neuropharmacology* 1986; 25(10): 1095-1101.
12. Ryder S, Way WL, Trevor AJ: Comparative pharmacology of the optical isomers of ketamine in mice. *Eur J Pharmacol* 1978; 49: 15-23.
13. Smith DJ, Pekoe GM, Martin LL, et al: The interaction of ketamine with opiate receptor. *Life Sci* 1980; 26: 789-795.
14. Finck AD, Nagai SH: Opiate receptor mediation of ketamine analgesia. *Anesthesiology* 1982; 56: 291-297.
15. De Simoni MG, Dal Toso G, Giglio R, et al: The effect of ketamine on the dopamine system, induction of tolerence and cross tolerence with morphine, in Kamenta JM, Domino EF, Geneste P(eds): *Phencyclidine and related Arylcyclo-*

hexamines. Present and Future Application, NPP Books, Ann Arbor, 1983, pp 485-493.
16. De Simoni MG, Giglio R, Dal Toso G, et al: Cross tolerence between ketamine and morphine to some pharmacological and biochemical effects. *Neuropharmacology* 1985; 24: 541-545.
17. Fratta W, Casu M, Balestri A, et al: Failure of ketamine to interact with opiate receptors. *Eur J Pharmacol* 1980; 61: 389-391.
18. Douglas BG, Dagirmangian R: The effect of magnesium deficiency on ketamine sleeping time in rat. *Br J Anesth* 1975; 47: 336-340.
19. Cumming JF: The development of an acute tolerance to ketamine. *Anesth Analg* 1976; 55: 788-791.
20. Benninger RJ: The role of dopamine in locomotor activity and learning. *Brain Res Rev* 1983; 6: 173-196.
21. Nakamura H, Kadokawa T, Nakatsuji K, et al: Pharmacological studies of a new antiinflammatory drug, 1-phenylsulfonyl-5, 5-diphenylhydantoin in experimental animals. *Arzneimittal-Forsch* 1970; 20: 1032-46.
22. Wiley JN, Downs DA: Lack of antagonism by naloxone of the analgesic and locomotor stimulant actions of ketamine. *Life Sci* 1982; 31: 1071-1075.
23. Pekoe GM, Smith KJ: The involvement of opiate and monoaminergic neuronal systems in the analgesic effects of ketamine. *Pain* 1982; 12: 57-73.
24. Gebhart GF: Recent developments in the neurochemical bases of pain and analgesia. *Natl Inst Drug Abuse Monogr Ser* 1983; 45: 19-35.
25. Basbaum Ai, Fields HL: Endogenous pain control systems. *Ann Rev Neurosci* 1984; 7: 309-338.
26. Yaksh TL, Rudy TA: Narcotic analgesics : CNS sites and mechanisms of action as revealed by intracerebral injection techniques. *Pain* 1978; 4: 299-359.
27. Cohen SR, Abbott FV, Melzack R: Unilateral analgesia produced by intraventricular morphine. *Brain Res* 1984; 303: 227-287.
28. Coderre TJ, Abbott FV, Melzack R: Effects of peripheral antisympathetic treatments in the tail flick, formalin and autotomy tests. *Pain* 1984; 18: 13-23.
29. Tyers MB: A classification of opiate receptors that mediate antinociception in animal. *Br J Pharmacol* 1980; 69(3): 503-512.
30. Abbott FV, Franklin KB: Noncompetitive antagonism of morphine analgesia by diazepam in the formalin test. *Pharmacol Biochem Behav* 1986; 24(2): 319-321.
31. Ahlenius S, Engel J, Zoller M: Effects of apomorphine and haloperidol on exploratory behavior and latent rearing in mice. *Physiol Psychol* 1977; 5: 290-294.

=국문초록=

Ketamine에 의한 진통작용과 행동변화에 대한 연구

계명대학교 의과대학 약리학교실

김수경 · 이성룡

Ketamine은 해리성 마취제로서 널리 이용되고 있으며, 마취용량에서 행동변화가 초래되며, 수면용량이내에서는 진통효과가 있다고 한다. 이러한 ketamine의 작용기전에 대하여 opioid 수용체가 관련된다고 하는 보고들이 있으며, 반면 이에 상반되는 보고들도 있다. 저자는 이미 ketamine에 의한 뇌내 catecholamine함량의 변동을 실험해 본 바 있기에, 본 연구에서는 뇌내 monoamine함량의 변동을 초래하는 약물 몇종과 opioid 길항제인 naloxone을 사용하여 진통작용, 자발성 운동, 상동운동의 변화를 관찰하고자 하여 다음과 같은 결과를 얻었다. 복강내로 ketamine 20mg/kg 또는 80mg/kg를 투여하여 진통효과및 자발성 운동의 증가를 관찰하였다. Ketamine의 진통작용은 naloxone 이나 haloperidol에 의해 억제되었으나, apomorphine, reserpine, α-methyl-para-tyrosine(α-MPT)에 의해 별 변화가 없었다. Ketamine의 자발운동의 증가는 naloxone에 의해 변화가 없었으며, apomorphine에 의해서는 다소, reserpine, haloperidol 또는 α-MPT에 의해서는 유의하게 억제되었다. 상동운동 변화에 대해서는 naloxone 또는 apomorphine은 별 변화를 일으키지 못했으나, α-MPT, reserpine, haloperidol에 의해서는 유의한 증감을 나타내었다.

이상의 결과로 보아, ketamine의 진통작용은 opioid 수용체에 기인되며, 자발운동및 상동운동은 뇌내 monoamine계에 더 기인되는 것으로 사료된다.

=Abstract=

A Study on the Ketamine-induced Analgesia and Locomotor Activity in Mice

Department of Pharmacology, School of Medicine, Keimyung University, Taegu

Soo Kyung Kim, MD; Seong Ryong Lee, MD

Ketamine produced an analgesia at subhypnotic doses in the absence of significant behavioral effect. Ketamine also produces a variety of behavioral change at anesthetic dose. The analgesia produced by ketamine has been known to ascribed to interaction with opioid receptors. The recent studies have shown that ketamine interferes with metabolism of brain monoamines. In this connection, to elucidate further the mechanism of analgesic action, locomotor activity and stereotyped behavior of ketamine, we have examed the effect of naloxone(5mg/kg), apomorphine(400μg/kg), haloperidol(200μg/kg), reserpine(5mg/kg) and α-methyl-p-tyrosine(α-MPT, 250mg/kg) on the analgesia and behavioral change of ketamine.

In this study, we were obtained that ketamine(20mg/kg or 80mg/kg i.p) caused a dose-dependent increase in tail-flick latency(TFL) and moderate increase of locomotor activity and slight change of stereotyped behavior. The analgesic action of ketamine(80mg/kg) was inhibited by naloxone or haloperidol and not affected by apomorphine, reserpine or α-MPT. The increase of locomotor activity of ketamine(20mg/kg or 80mg/kg) did not affected by naloxone, moderately inhibited by apomorphine and significantly by reserpine, haloperidol, or α-MPT. The stereotyped behavior of ketamine(20mg/kg or 80mg/kg) was not affected by naloxone or apomorphine and significantly inhibited by reserpine or α-MPT and increased by haloperidol.

These results suggests that analgesia of ketamine may be due to opioid receptor and locomotor activity or stereotyped behavior was influenced by brain monoaminergic system partially.

Key Words : Analgesia, Behavioral change, Ketamine