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Interactive effects of morphine and scopolamine, MK-801, propanolol on spatial working memory in rhesus monkeys

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HIGHLIGHTS

- Interactive effect of morphine + scopolamine (MK-801, propanolol) on monkey's memory.
- Morphine + scopolamine deteriorated spatial working memory.
- Morphine + MK-801 restored impairment caused by morphine and MK-801.
- Morphine (0.01 mg/kg) + propranolol reversed impaired memory induced by single drug.

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ABSTRACT

Opiate, cholinergic, glutamatergic and beta-adrenergic neurotransmitters play key roles in learning and memory in humans and animals. Dysfunction of the interactions between these neurotransmitters may induce human diseases. In the present study, the interactions of morphine and acetylcholine (ACh), NMDA, and beta-adrenergic receptor antagonist (scopolamine, MK-801, and propanolol) were evaluated in a single-blind design by co-administrations of morphine and these drugs in a delayed response in rhesus monkeys. The results indicated that: (1) Co-administration of morphine and scopolamine deteriorated spatial working memory. (2) Co-treatment of morphine and MK-801 restored impairment caused by morphine and MK-801 in a dose-depending pattern. (3) Morphine plus propranolol impaired spatial working memory. High dose of morphine (0.01 mg/kg) reversed impaired spatial working memory induced by single propranolol and morphine treatment. These data suggested that the interactions of morphine and AChergic, NMDAergic and beta-adrenergic compounds were involved in spatial working memory in rhesus monkeys.

1. Introduction

Working memory refers to the short-term storage and manipulation of items in memory and is thought to be dependent upon the prefrontal cortex PFC [4]. PFC is modulated by a number of neurotransmitters such as dopamine [19], noradrenaline (NE), Ach [21] and NMDA [15].

Morphine influenced memory in animals through agonizing the μ opioid receptors which was generally distributed in mammal brain including PFC [23]. Morphine induced deficits in working memory and episodic memory in humans and rhesus monkeys [14,22]. Our previous data indicated that heroin caused deficits in both map and landmark working memory in addictive humans [25] and morphine impaired mice spatial recognition memory [16]. Recently we found that morphine impaired spatial working memory in a delayed response task which depends on morphine doses (Fig. 1).

Like opioid receptors, AChergic, NMDAergic and beta-adrenergic receptors are richly spread in the mammalian brain, and blocking or activating these receptors have been shown to influence learning and memory in humans and animals. Interactions of the opiate system and these three neurotransmitters may exist and contribute to the learning and memory.

The muscarinic ACh receptors of the ventral tegmental area played an important role in morphine-induced recovery of memory [7]. Our previous study found that scopolamine enhanced the extinction of morphine-induced conditioned place preference in mice depending on morphine exposure time [24]. In the present study, we used a muscarine receptor ACh antagonist scopolamine to test the effect of the co-treatment with morphine on working memory in rhesus monkeys.

Studies of co-administration with NMDA drugs and morphine in mice found that NMDA receptors might be involved, at least in part, in morphine state-dependent learning in mice [28]. The

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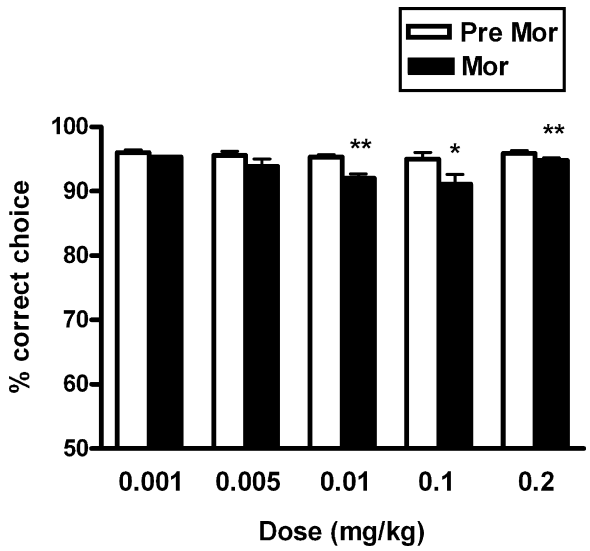

Fig. 1. Morphine (Mor) treatment impaired working memory when compared with performance on the day before drug treatment (Pre Mor) (**$P < 0.01$, *$P < 0.05$).

non-selective NMDA receptor antagonist MK-801 (dizocilpine) has been shown to suppress not only physical but also psychological dependence produced by morphine [18]. NMDA receptor antagonists LY235959 potentiated the antinociceptive effects of morphine in squirrel monkeys [1].

Using a Y-maze test, our previous study found that co-administration with morphine and beta-adrenergic receptor antagonist propranolol disrupted the consolidation of spatial recognition memory, suggesting that inactivation of the beta-adrenergic system may contribute to morphine-induced impairment of memory [29].

Interactions of the opiate and AChergic, NMDAergic and beta-adrenergic systems were widely studied in rodents. However, few were found in monkeys. Because the monkeys are close species to human in intelligence, thus, in the present study, we evaluated effects of co-administration of morphine and ACh, NMDA and beta-adrenergic compounds on memory in rhesus monkeys. Meanwhile, each compound was also tested single. We tested the spatial working memory in rhesus monkeys by using a WGTA (The Wisconsin General Test Apparatus) delayed response task which is a marker task for working memory [11].

Since in our recent study, we found that morphine at doses of 0.01, 0.1 and 0.2 mg/kg impaired the spatial working memory in the WGTA task. However, lower doses of morphine (0.001 and 0.005 mg/kg) did not have a significant effect on working memory (Fig. 1). Thus, we chose two low doses of morphine (Mor 0.01 and 0.001 mg/kg) to test the effect of the co-treatments on the spatial working memory. Mor 0.01 mg/kg impaired working memory while the lower dose (0.001 mg/kg) had no effect on working memory. We used low doses of morphine and other compounds in order to avoid the development of opiate tolerance and allowed monkeys to recover from the drug treatments quickly.

2. Methods

2.1. Animals

Four male rhesus monkeys (*Macaca mulatta*) from the breeding colonies at the Kunming Institute of Zoology (KIZ) were used. Monkeys were 8.0 ± 0.7 years and weighed 6.8 ± 0.3 kg at the beginning of the experiment. After the experiment finished, the average monkeys' weight was 9.0 ± 0.8 kg. One monkey was replaced because his performance scores were too high to discriminate the effects of the study after one-year of test.

Monkeys were housed singly under standard conditions (a 12-h light/dark cycle with light on from 07:00 to 19:00 h, humidity at 60%, temperature at $21 \pm 2\,^{\circ}C$) in the animal house. During the experimental period, monkeys were fed once per day, the normal regimen being twice daily.

The experiments were conducted in accordance with the guidelines for the National Care and Use of Animals approved by the Chinese National Animal Research Authority.

2.2. Drugs

Individual drugs were purchased directly from the following suppliers: morphine hydrochloride, 10 mg/1 ml per ampule (Sheng Yang-the 1st Medical Company, China). MK-801 and propranolol (Sigma, USA). Scopolamine hydrobromide (ShangHai HeFeng Medical Company, China). Dosing increases were stopped if observations in the monkey's behavior changed. Saline solutions (0.9% NaCl) of the drugs were made fresh in the afternoon prior to the injection day and stored at $4\,^{\circ}C$ overnight.

2.3. Behavioral tests

2.3.1. Apparatus

The WGTA was a wooden box (length: 70 cm, width: 45 cm, height: 110 cm) with a small window for experimenter observing and a light (25 W) inside. There was a wooden gate behind the box which could be lifted up and lowered down through a pulley by the experimenter. When the wooden gate was lifted, the monkey could see the experimenter put one peanut into one of the two wells (diameter 3.5 cm, between distance was 8 cm) which were horizontally arrayed on a wooden plate in front of him. Immediately after the monkey saw the placement of the peanut, two pieces of white plastic panels ($10\,cm \times 10\,cm$) were placed on two wells to cover them and the gate was lowered down to block the monkey's sight for a delayed duration. After a delayed time, the gate was lifted up and the wooden plate with the wells became visible to the monkey. The monkey was allowed to choose the peanut from one of two covered wells by his hands.

A single-blind procedure was used. The same experimenter gave the injections and ran the delayed response experiments without knowing on which day what kind of compounds were given to the monkeys.

2.4. Behavioral procedures

Each monkey had to be trained around 1000 trials before the pharmacological experiments started, 30 trials for each work day. The peanuts were placed into the right or left well for 15 trials each day. The placement of peanut was quasi-randomly arranged [3].

Five different delay lengths (A–E) were semi-randomly distributed over these 30 trials in each session for every monkey. $A = B \times 0 = 0$ s, $B = B \times 1 = B$ s, $C = B \times 2 = 2B$ s, $D = B \times 3 = 3B$ s, and $E = B \times 4 = 4B$ s. B delay length for each monkey increased from $B = 0$ s at the training before the pharmacological experiment started. After the monkey became familiarized to the task, the B delay length was increased by 3–5 s if the monkey scored more than 93% correct responses (correctly chose 28 out of 30 trials) for continuous three days. Once the performance was stable at more than 93% correct responses at an optimum B, the pharmacological study was started.

B delay length of monkeys was 11.3 ± 6.3 s in average at the beginning of the pharmacological experiment, and 20.5 ± 6.1 s when the experiment ended.

When the monkeys correctly chose more than 93% for 3 days on a row, they were intra-muscularly (i.m.) injected with saline

30 min before the test, and after 30 min, the monkeys were tested in the delayed response task as a baseline which was marked as the Pre-treatment.

The monkeys were i.m. injected with different compounds 30 min before the test on the next day. After 30 min, they were tested in the delayed response task. The following tests usually were conducted on the next day in order to measure if the monkey's performance was recovered to the normal level, which was marked as Post-treatment.

The volume of the drugs and saline was 0.05 ml/kg body weight. Usually, the monkey was injected with saline on Monday followed by drugs on the next day and allowed to recover for a few days which meaning subjects returned to 93% correct responses between drugs treatment. Most doses of drugs were repeatedly administrated for 2–5 times randomly, drugs with different doses were tested randomly during the period of the experiments.

2.5. Statistical analysis

Data were expressed as mean percentage of the correct responses on each day (mean ± SEM). Differences between the drug treatments and Pre-treatment were assessed with an ANOVA, while a two-way ANOVA with repeated measures was used to analyze the difference between the co-treatment and the single treatment. Differences between treatments were considered significant when $P \leq 0.05$.

3. Results

3.1. Effects of co-administration of morphine (Mor) and scopolamine (Scop) on spatial working memory in rhesus monkeys

Drug treatment decreased the working memory (main effect of drug: $F(1,2) = 280.8$, $P = 0.004$, within effect of drug: $F(5,10) = 39.5$, $P < 0.001$, interaction drug × treatment: $F(5,10) = 43.7$, $P < 0.001$).

As shown in Fig. 2, single treatment of Scop 0.01 and 0.02 mg/kg impaired the spatial working memory, as reflected by a lower percentage of correct choices than performance on the day before and after the treatment. Scop 0.02 mg/kg seriously affected monkeys' behaviors by increasing their locomotor activities so that only one monkey could finish the task. Thus, we chose Scop (0.01 mg/kg) to test the co-treatment effects.

Monkeys injected with Scop (0.01) + Mor (0.001) scored lower in working memory than before and after the treatment, also than under Mor (0.001 mg/kg) treatment alone or Scop 0.01 mg/kg alone.

Scop (0.01) + Mor (0.01) decreased working memory when compared with performance before and after the treatment, and when compared with the treatment of Mor 0.01 mg/kg alone, or Scop 0.01 mg/kg alone.

Three monkeys became hyperactive after co-administration of Scop (0.01 mg/kg) and Mor (0.01 mg/kg). Two monkeys became hyperactive after co-treatment of Scop (0.01 mg/kg) and Mor (0.001 mg/kg).

3.2. Effects of co-administration of Mor and MK-801 on spatial working memory in rhesus monkeys

Drug treatment decreased the working memory (main effect of drug: $F(1,2) = 22.3$, $P = 0.04$, within effect of drug: $F(11,22) = 25.3$, $P < 0.001$, interaction drug × treatment: $F(11,22) = 17.8$, $P < 0.001$).

Fig. 3 shows that single treatment of MK-801 (0.02 and 0.04 mg/kg) impaired spatial working memory when compared with performance before the treatment while MK-801 at doses of 0.005 and 0.01 mg/kg had no effects.

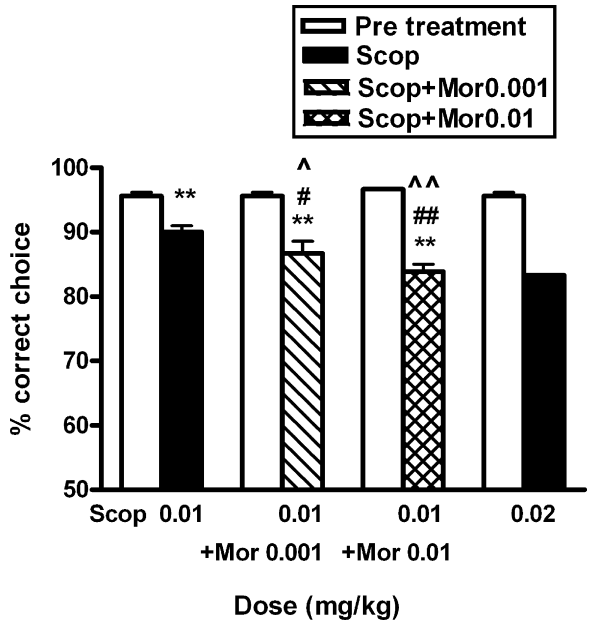

Fig. 2. Single scopolamine (Scop) treatment and Mor + Scop impaired working memory when compared with performance on the day before drug treatment (Pre-treatment) (**$P < 0.01$). Drug co-treatment deteriorated the impaired working memory produced by single Mor ($^{\#\#}P < 0.01$, $^{\#}P < 0.05$) and single Scop treatment ($^{\wedge\wedge}P < 0.01$, $^{\wedge}P < 0.05$). Only one monkey finished the task 30 min after injection with Scop at dose of 0.02 mg/kg.

Two monkeys decreased their motor activities after injection with MK-801 (0.02 mg/kg). All three monkeys moved slowly and could not sit stable after injection of MK-801 0.04 mg/kg. One monkey could not finish the delayed response task.

MK-801 (0.04) + Mor (0.001) decreased percentage of correct choice when compared with performance on the day before and after the treatment, but ameliorated the impaired memory induced by MK-801 0.04 mg/kg alone.

MK-801 (0.02) + Mor (0.001) also decreased spatial working memory but failed to obtain a significant difference due to two subjects could finish the task.

Interestingly, although MK-801 (0.02) + Mor (0.001) tended to impair working memory, MK-801 (0.02) + Mor (0.01) increased spatial working memory when compared with single treatment of Mor 0.01 mg/kg, and single treatment of MK-801 0.02 mg/kg. All three monkeys could finish the task after co-injections.

MK-801 (0.04) + Mor (0.01) seriously influenced two monkeys' behaviors by decreasing their locomotor activity. The monkeys could not get food successfully with their hands and could not sit and stand stable by themselves so that they quitted the task. Thus, only one monkey finished the delayed response under the co-treatment.

3.3. Effects of co-administration of Mor and propranolol (Pro) on spatial working memory in rhesus monkeys

Drug treatment decreased the working memory (main effect of drug between Pre-treatment and treatment: $F(1,4) = 36.5$, $P = 0.004$, within effect of drug: $F(12,48) = 3.6$, $P = 0.001$, interaction drug × treatment: $F(12,48) = 4.1$, $P < 0.001$).

Single treatment of Pro at middle doses (0.01, 0.05 and 0.1 mg/kg) impaired monkeys' spatial memories, while low dose (0.005 mg/kg) and high dose (0.5 mg/kg) had no effect (Fig. 4).

Most co-treatments of Mor and Pro impaired spatial working memory when compared with performance before and after co-treatments.

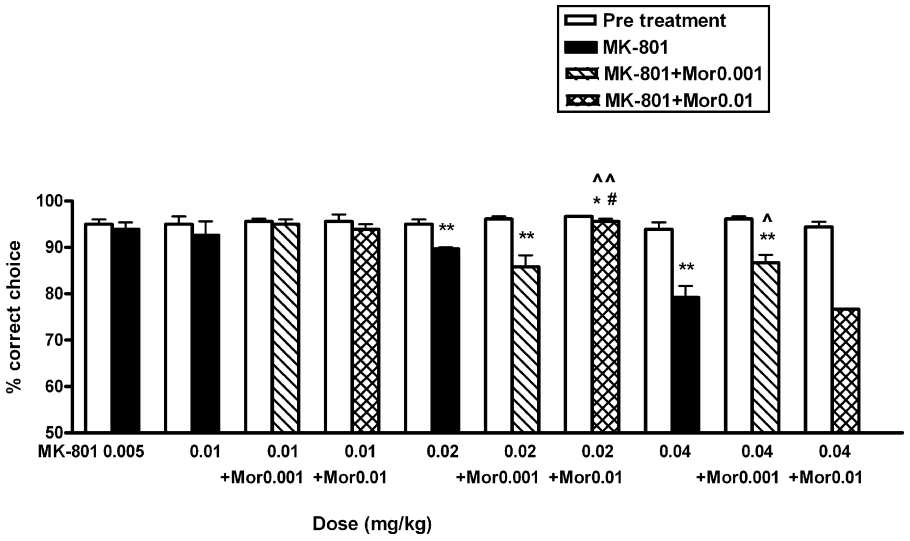

Fig. 3. Effects of MK-801 and Mor + MK-801 on working memory. Drug treatment impaired working memory when compared with Pre-treatment ($^{**}P < 0.01$, $^{*}P < 0.05$). Drug co-treatment ameliorated memory under single Mor ($^{\#}P < 0.05$) and MK-801 ($^{\wedge\wedge}P < 0.01$, $^{\wedge}P < 0.05$).

Meanwhile, Pro (0.01, 0.05) + Mor (0.001) decreased the correct scores when compared with the performance under morphine treatment.

Similarly, Pro (0.005, 0.01) + Mor (0.01) impaired working memory. Pro (0.01, 0.05) + Mor (0.01) reversed morphine induced impairment in working memory. Additionally, Pro (0.05) + Mor (0.01) ameliorated impaired memory produced by single Pro treatment.

Single Pro and co-treatments did not seriously affect monkey's behavior.

4. Discussion

The current study found that Scop, MK-801 and Pro all impaired the spatial working memory of rhesus monkeys but depending on the doses. In addition, Mor + Scop deteriorated spatial working memory. Mor + MK-801/Mor + Pro restored impairment caused by Mor and MK-801/Pro in a dose-depending pattern.

Block of ACh receptors by Scop has been shown to cause deficits in various types of memory [8]. A similar result was found in our current study. In addition, the co-treatment of Mor and Scop deteriorated working memory in monkeys. Morphine injection decreased the turnover rate of acetylcholine in neocortex and hippocampus while the opiate antagonist naloxone reversed this effect [27]. Opiate receptor antagonists increased cholinergic function, whereas opiate agonists decreased the ACh in the brain. The interaction of morphine and cholinergic system occurred in the central nervous system [13]. Thus, both Mor and Scop reduced ACh in brain which may worse working memory as shown in the current study. This result is consistent with the hypothesis that morphine may influence memory also through its effect on the cholinergic system.

The hyperactivity produced by Scop was not changed after the co-treatment of Mor, which also suggested that Mor did not reverse the ACh antagonist's effects in behavior. The current results were partly consistent with our previous studies which indicated that Mor enhanced the effects of cholinergic receptors antagonists Scop and atropine on Y-maze recognition memory and CPP in mice [24].

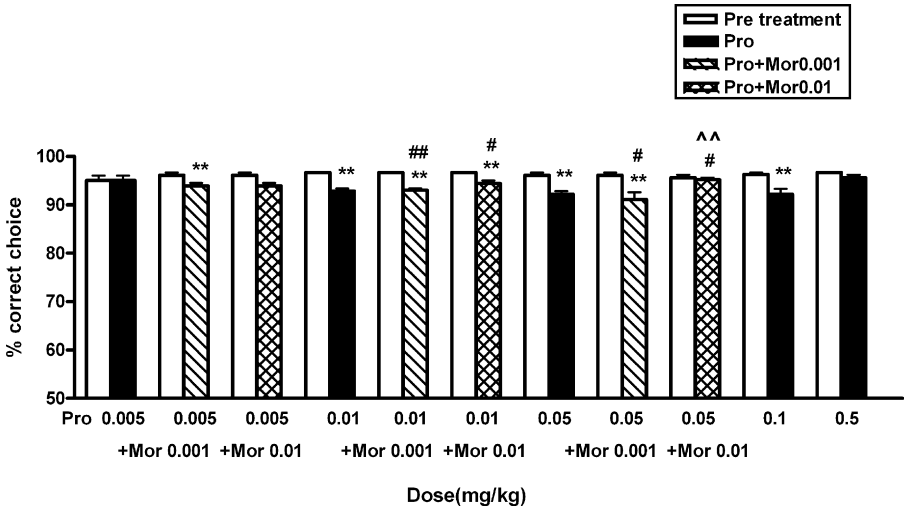

Fig. 4. Effects of propranolol (Pro) and Mor + Pro on working memory. Drug treatment impaired working memory when compared with Pre-treatment ($^{**}P < 0.01$). Pro (0.01, 0.05) + Mor (0.001) decreased memory under single morphine treatment ($^{\#\#}P < 0.01$, $^{\#}P < 0.05$). Pro (0.01, 0.05) + Mor (0.01) increased memory under single Mor treatment ($^{\#}P < 0.05$). Pro (0.05) + Mor (0.01) ameliorated memory under single Pro injection ($^{\wedge\wedge}P < 0.01$).

Blocking of NMDA receptors by a single treatment with MK-801 disrupted working memory in monkeys, a result that was consistent with the previous studies from our lab [26] and other groups [20]. Our data showed that Mor + MK-801 ameliorated spatial working memory and behavior but in a dose-dependent pattern. When MK-801 was co-injected with Mor at a low dose of 0.001 mg/kg, the impairment in working memory produced by MK-801 still existed, suggesting that Mor at low doses failed to reverse MK-801 induced impairment in working memory. In contrast, when MK-801 was combined with morphine at a high dose of 0.01 mg/kg, the impairment was suppressed, which was consistent with the memory studies in rodent under the NMDA antagonists [5]. We assumed that morphine at high dose restored the deficit induced by MK-801 by increasing the glutamate activity more efficiently than the low dose of Mor did.

From the behavioral observation, we also found that low dose of Mor (0.001 mg/kg) could not suppress behavioral damage in MK-801 treated monkeys, only two monkeys could go through the task. However, when co-administrated with a high dose of Mor (0.01 mg/kg), three monkeys could successfully finish the task. Only when MK-801 seriously affected the monkeys at the dose of 0.04 mg/kg, the high dose of Mor (0.01 mg/kg) failed to restore both behavior and memory.

Our current data confirmed that NMDA receptors contribute to the function of the opiate receptors and their signal transmission [10].

Beta-adrenergic receptors are rich in the intermediate layers of the PFC [12]. While working memory is dependent upon PFC, therefore, moderate levels of NE are thought to facilitate working memory [6]. Our finding that beta-blocker Pro impaired monkey spatial working memory was consistent with studies in humans [17].

When we chose three doses of Pro combined with Mor, poor performance could not be ameliorated by Mor. Additionally, co-treatment decreased correction scores when compared with Mor (0.001 mg/kg) alone. This result was consistent with our previous finding in mice [29]. Co-treatment with high dose of Mor (0.01 mg/kg) and Pro (0.05 mg/kg) did not show impaired memory, however ameliorated the impaired memory induced by Mor alone. The result suggested that Mor at high dose might reverse the effect of Pro but depending on the doses of both Mor and Pro.

Evidence suggests that effects of opiates on memory are mediated through the regulation of NE release in the cerebral cortex and amygdala [2]. Using high performance liquid chromatography (HPLC), Devoto et al. assumed that the change of extracellular dopamine in the PFC induced by morphine treatment may be explained by the fact that dopamine in the PFC mainly represents the amine co-released from NE terminals [9].

In the current study, co-administrations of morphine might reduce NE in the PFC while Pro blocked NE receptors which might lead to greater impairment in monkey's working memory. Regarding to the treatment of high dose of Mor 0.01 mg/kg and Pro (0.05 mg/kg), in contrast, improved working memory which may be explained by Mor induced dopamine release partly facilitating memory.

There is a disadvantage of the WGTA which cannot account for the possible effects of the compounds on movement, attention and appetite in the monkeys. These effects could not be excluded from the study, which limited the maximum dosages of the compounds used to low and safe levels to protect the monkeys from any extraneous effects from the drugs.

Since rhesus monkeys were evolutional close to humans, thus, the data give insight into the relationships between opiate and these neurotransmitters, also supports possible therapy in human addiction.

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