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ARE GLYCINE$_B$ SITES INVOLVED IN THE DEVELOPMENT OF MORPHINE TOLERANCE?

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Are glicyne$_B$ sites involved in the development of morphine tolerance?
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Numerous data have indicated that competitive and non-competitive N-methyl-D-aspartate (NMDA) receptor antagonists attenuate the development of tolerance to the analgesic effect of morphine. This study extends these findings on the effects of glycine$_B$ site antagonist, L-701.324. Tolerance to the analgesic effect of morphine was measured in hot-plate test in Wistar rats. For 9 days, animals were first injected with vehicle or glycine$_B$ receptor antagonist, L-701.324 (2.5 and 5 mg/kg, *po*). The non-competitive NMDA receptor antagonist, MK-801 (0.05 or 0.1 mg/kg, *ip*) was used as a reference compound. The injection of L-701.324, MK-801 or saline was followed, 20 min later, by the injection of morphine (10 mg/kg, *sc*). Hot-plate latencies were determined 20 min after the second injection on odd-numbered days. The results indicated that chronic administration of glycine$_B$ site antagonist, L-701.324 decreased the analgesic effect of morphine and they may suggest that this substance at both used doses increased the development of morphine tolerance, whereas non-competitive NMDA antagonist, MK-801 at the dose of 0.1 mg/kg potentiated the analgesic effect of morphine and attenuated the development of morphine tolerance.

Key words*: morphine, tolerance, NMDA antagonists, hot-plate test, rats*

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INTRODUCTION

Tolerance to and dependence on morphine are characteristic features of chronic administration of this drug. In the clinical therapy of pain, the rapid development of morphine tolerance leads to a need to increase its dose in order to maintain the desired effect. On the other hand, dependence and tolerance are in most cases connected with the abuse of the drug, overdosing of which may lead to death.

Numerous studies suggest that the activation of N-methyl-D-aspartate (NMDA) receptors plays a role in the development of opioid tolerance, dependence and withdrawal syndrome. For example, competitive and non-competitive NMDA receptor antagonists appear to block development of tolerance to antinociceptive effect of morphine [1, 4, 5, 11, 12, 23], and suppress the development of morphine dependence and withdrawal syndrome [13, 32].

It is now generally approved that glycine is required for the activation of an NMDA receptor [15] and NMDA/glycine (glycine$_B$) site antagonists are devoid of many undesirable "side-effects" characteristic of competitive and non-competitive NMDA receptor antagonists, which preclude their potential clinical use (for review see [8]). Thus, another pharmacological approach to prevent the morphine tolerance, dependence and withdrawal syndrome would be possible by antagonism of glycine$_B$ sites.

In the present study, L-701.324, a centrally bioavailable glycine$_B$ site antagonist, was used to test the influence of this substance on the development of morphine tolerance. The results were compared to those obtained after administration of a non-competitive NMDA receptor antagonist, MK-801, which was used in the present study as a reference compound, reported previously to inhibit the development of morphine antinociceptive tolerance in rats [32].

MATERIALS and METHODS

Animals

The experiments were carried out on male Wistar rats (HZL, Warszawa, Poland) performed in agreement with ethical regulations and were approved by the local Ethics Committee. The animals (180–230 g) were housed in plastic cages in groups of four per cage, and had unlimited access to food and water. The rats were kept under conditions of constant temperature (25°C), and controlled light-dark cycle (light on between 7 a.m. and 7 p.m.).

Morphine tolerance

Tolerance to the analgesic effects of morphine (associative tolerance) was induced according to the method described by Trujillo and Akil [32]. For 9 days, the rats were taken to the experimental room each morning, and after at least 15 min of habituation, they were weighed. Every day animals received one injection of vehicle, glycine$_B$ site antagonist, L-701.324 (2.5 and 5 mg/kg) or non-competitive NMDA receptor antagonist, MK-801 (0.05 or 0.1 mg/kg), and 20 min later they were injected with morphine (10 mg/kg). The development of tolerance to analgesic effect of morphine was determined 20 min after the second injection on the odd-numbered days. In the hot-plate test, rats were placed on warmed surface (Porfex, Białystok, Poland) heated to 56°C [34] and latency to avoidance or withdrawal behavior (foot lifting or jumping) to the thermal stimulus was determined. The maximum time score was 20 s to minimize tissue damage. Each animal that failed to respond within 20 s (cut-off time) was removed from the apparatus and assigned a latency of 20 s. Additionally, on day 10 of the experiment, the first injection was omitted and all groups of rats received 10 mg/kg of morphine except for the saline-saline group, which was given saline instead. Hot-plate test was performed 20 min later.

Drugs

The glycine$_B$ site antagonist, L-701.324 ([7-chloro-4-hydroxy-3-(3-phenoxy)-phenyl-2(*H*)quinolone], Merck Sharp & Dohme, Rahway, USA) was given as a suspension, prepared using 0.5% solution of methylcellulose. The non-competitive NMDA receptor antagonist, MK-801 ([(+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten5,10-imine maleate], RBI, Natick, USA) and morphine HCl (Polfa, Kutno, Poland) were dissolved in physiological saline.

L-701.324 was administered per os (*po*), as per os administration of the substance gives the least undesirable "side-effects" [6], in a volume of 5 ml/kg, MK-801 was administered intraperitoneally (*ip*), and morphine was given subcutaneously (*sc*) in a volume of 2 ml/kg.

Data analysis

Data were reported as means ± SEM. The significance of the differences in the mean responses to a test dose of morphine in the experiments estimating the development of morphine tolerance was determined by the analysis of variance (two-way ANOVA) and *post-hoc* confirmation with the Newman-Keul's test. The data obtained on day 10 of the experiment were analyzed by one-way analysis of variance (one-way ANOVA) with comparisons between groups. *Post-hoc* comparisons were carried out by the Newman-Keul's test. The $p < 0.05$ was considered to be statistically significant.

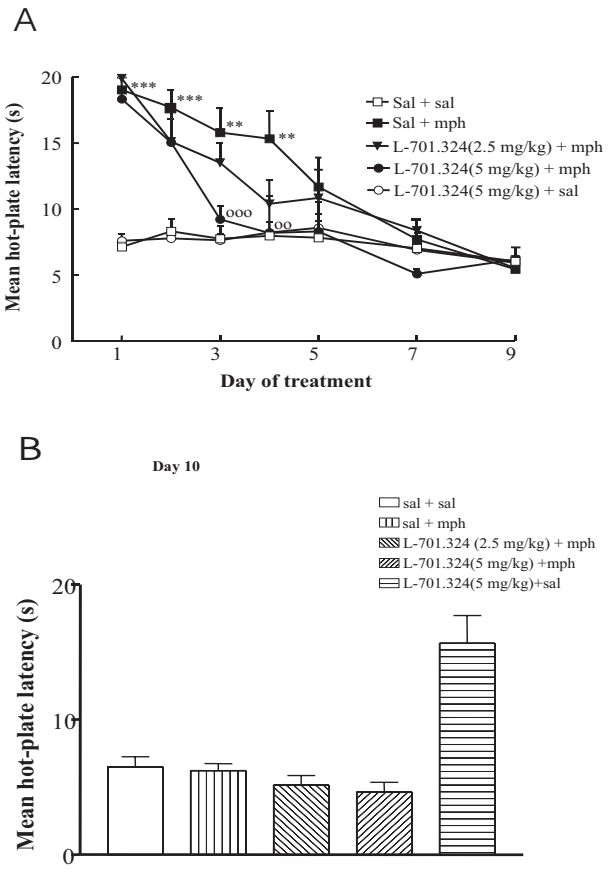

Fig. 1. The influence of glycine$_B$ site antagonist L-701.324 on the development (A) and expression (B) of morphine tolerance in the hot-plate test in rats. (A) Hot-plate latencies were assessed 20 min after acute morphine injection (10 mg/kg) in rats repeatedly challenged with morphine (mph; 10 mg/kg; *sc* once a day, 9 days). L-701.324 (2.5 and 5.0 mg/kg, *po*) was given 20 min before every morphine injection. ***$p < 0.001$; **$p < 0.01$ *vs*. control (sal-sal) group; $^{ooo}p < 0.001$; $^{oo}p < 0.01$ *vs*. mph– sal group (Newman-Keul's test). The expression of morphine tolerance was assessed on day 10 (B) when the first injection was omitted and all groups received morphine (10 mg/kg, *sc*) except control (sal-sal). The bars indicate the treatment, the animals received on days 1–9. On day 10 there was no significant difference between L-701.324– mph and sal-mph groups. Values are means ± SEM of 6–7 rats in the group

RESULTS

The influence of glycine$_B$ antagonist on the development of tolerance to analgesic effect of morphine in hot-plate test in rats

Acute treatment with morphine (10 mg/kg, *sc*) following repeated treatment with vehicle injections once a day produced significant analgesia $F_{(1, 109)} = 76.72$, $p < 0.001$ in hot plate test (two-way ANOVA). *Post-hoc* analysis showed development of tolerance after 5 days of morphine injections (Fig. 1, A). Glycine$_B$ site antagonist, L-701.324 given chronically once a day for 9 days, 20 min before each morphine injection, decreased the analgesic effect of morphine which may suggest more rapid development of tolerance to analgesic effect of morphine [2.5 mg/kg, *po* ($F_{(1, 112)} = 1.31$, $p > 0.05$); 5 mg/kg, *po* ($F_{(1,103)} = 20.41$, $p < 0.001$)]. The *post-hoc* analysis revealed that the morphine antinociception was reduced by the dose of 5 mg/kg of L-701.324 on the day 3 ($p < 0.001$) and 4 ($p < 0.01$) of the experiment (Fig. 1 A). On the day 10 of experiment, when the first injection was eliminated and animals received only morphine, there were no significant differences between morphine-saline- and L-701.324-morphine-treated groups (Fig. 1 B).

The influence of MK-801 on the development of tolerance to analgesic effect of morphine in hot-plate test in rats

The data in Figure 2 revealed that daily morphine injections (10 mg/kg, *sc*) for 9 days induced analgesic effect in rats [$F_{(1, 80)} = 23.25$, $p < 0.001$ (two-way ANOVA)]. *Post-hoc* analysis indicated the significant results on the day 1 ($p < 0.001$), 2 ($p < 0.01$) and 3 ($p < 0.05$) of morphine injection (morphine *vs.* control group). The non-competitive NMDA receptor antagonist, MK-801 had no effect on the development of morphine tolerance (two-way ANOVA) at the dose of 0.05 mg/kg, *ip* ($F_{(1, 88)} = 3.47$, $p > 0.05$) and strongly potentiated the analgesic effect of morphine at the dose of 0.1 mg/kg, *ip* ($F_{(1, 88)} = 45.62$, $p < 0.001$). *Post-hoc* analysis demonstrated that pretreatment of rats with MK-801 at the dose of 0.1 mg/kg caused enhancement of morphine analgesic effect, starting from the day 2 of

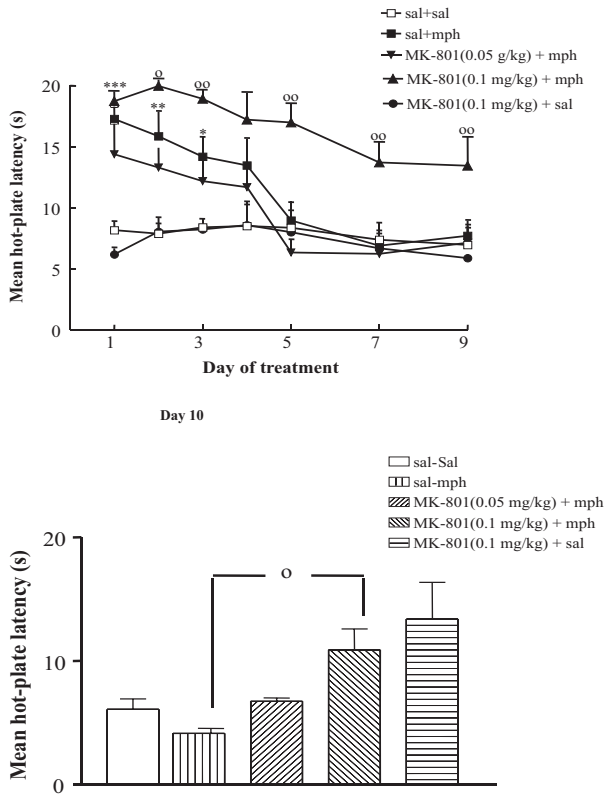

Fig. 2. The influence of the non-competitive NMDA antagonist, MK-801 on the development (A) and expression (B) of morphine tolerance in the hot-plate test in rats. (A) Hot-plate latencies were assessed 20 min after acute morphine injection in rats (repeatedly challenged with mph; 10 mg/kg; *sc* once a day, 9 days). MK-801 (0.05 and 0.1 mg/kg, *ip*) was given 20 min before every morphine injection. ***p < 0.001; **p < 0.01; *p < 0.05 vs. control (sal-sal) group; ^{o}p < 0.05; ^{oo}p < 0.01 vs. sal-mph group (Newman-Keul's test). (B) The bars indicate the treatment, the animals received on days 1– 9. The expression of morphine tolerance was assessed on day 10 when the first injection was omitted, and all groups received only morphine (10 mg/kg, *sc*) except control (sal-sal) group. ^{o}p < 0.05 vs. mph-sal treated group (Newman-Keul's test). Values are means ± SEM of 6–7 rats in the group

the experiment until the day 9 (Fig. 2 A). The NMDA receptor antagonist used alone had no effect on analgesia. On the day 10, when the first injection (MK-801) was omitted, the rats previously treated with MK-801 and morphine showed greater analgesia (less tolerance) than the animals repeatedly treated with saline and morphine (p < 0.05) (Fig. 2 B).

DISCUSSION

In present studies, glycine$_B$ site antagonist L-701.324 (5 mg/kg) given 20 min before morphine for 9 days decreased the analgesic effect of morphine in hot-plate test in rats, and this effect was observed since day 2 of the experiment. The attenuation of the analgesic effect of morphine may suggest that L-701.324 increased the development of tolerance to antinociceptive effect of morphine in hot-plate test in Wistar rats. The effect of non-competitive NMDA receptor antagonist, MK-801 at the dose of 0.1 mg/kg, was opposite to the effect of the glycine$_B$ site antagonist L-701.324 and indicated the attenuation of development of morphine tolerance and even potentiation of its analgesic effect.

As there is little evidence that NMDA receptor antagonists acting at the glycine$_B$ site attenuate the development of tolerance to morphine analgesia [3, 16, 22, 24], the effect of the non-competitive or competitive NMDA receptor antagonists is not convincing so far. For example, the experiments described by Belozertseva et al. [3] indicated that short-acting glycine$_B$ site antagonist, MRZ 2/576 significantly retarded the development of morphine tolerance in tail-flick test in mice only when it was given 120 and 150 min after each of the repeated morphine injections for an 8-day period and required injection of probenecid to extend its time of action. This substance did not affect the development of morphine tolerance when administered immediately, or at other time after morphine injection. In the experiments carried out on mice described by Lutfy et al. [22, 24], morphine was given within 1 min after a glycine$_B$ site antagonist, ACEA-1328. On the basis of those and my experiments, it is visible that the time of injection of glycine$_B$ site antagonists is crucial to their influence on the development of tolerance to morphine analgesic effect. Generally, although glycine$_B$ site antagonists are devoid of side-effects characteristic of non-competitive or competitive NMDA antagonists, they have poor penetration into the brain or limited solubility (for review see [8]). L-701.324 is a full glycine$_B$ site antagonist with good penetration into the brain and long $T_{1/2}$ (in the brain of ~ 2 h) [6]. In our previous studies, L-701.324 inhibited the development of morphine and ethanol dependence [18, 19]. In the present study, L-701.324 facilitated the development of tolerance to analgesic effect of morphine, when given 20 min before morphine injection as demonstrated in the hot-plate test in rats (Fig. 1). Although the influence of the substance on locomotor activity may hinder the interpretation of re-

sults in the hot-plate test, L-701.324 does not influence locomotor activity of rats at the used doses (2.5 and 5 mg/kg, *po*) in contrast to non-competitive NMDA receptor antagonist, MK-801, which indicated tendency to increase the locomotor activity in rats at the dose of 0.1 mg/kg, *ip* [19].

The decreasing influence of the non-competitive NMDA antagonist, MK-801, on development of tolerance to analgesic effect of morphine is very well documented (for review see [31]). However, it seems possible that undesirable side effects induced by this substance, e.g. psychotomimetic effects, ataxia, cognitive impairment [33], may delay the reaction of rats (foot lifting or jumping) in the hot-plate test. However, the data obtained on day 10, when the first injection (MK-801) was omitted, indicated that MK-801 lowered the development of tolerance to morphine antinociceptive effect in hot-plate test.

Studies concerning the influence of NMDA receptor antagonists on morphine tolerance were mostly performed in tail-flick test (for review see [31]). It is well known that behavioral response to both noxious stimuli (tail-flick and hot-plate tests) originate at different neuronal levels. The behavioral tail withdrawal response is predominantly a spinal reflex [10] but painful stimulation of the hind paw (hot-plate test) is under supraspinal control and probably involves neuronal pathways originating mainly in the midbrain and medullar structures [14]. Morphine induced antinociceptive effect independently of whether it was given intracerebroventricularly or intrathecally in both tail-flick and hot-plate tests [21]. There are also interactions between NMDA and opioid receptors in opioid-induced antinociception and tolerance (for review see [25]). It is rather unlikely that NMDA receptor antagonists block morphine antinociception at the level of the opiate receptors because they do not bind to the μ-opioid receptors [30]. Opioid receptors (μ) and NMDA receptors are co-localized on synaptic membranes in the dorsal horn and periaqueductal gray matter [7]. Spinella et al. [29] indicated that supraspinal morphine analgesia (from periaqueductal gray, PAG) was reduced by competitive and non-competitive NMDA receptor antagonists given to rostral ventromedial medulla in tail-flick test, and Kozela et al. [20] reported that non-competitive NMDA receptor antagonists with low affinity, given systemically, potentiated morphine-induced antinociception in tail-flick but not in hot plate test. However, probably the density of opioid and NMDA receptors as well as the differences in subunit composition of NMDA receptors in supraspinal structures and type of analgesic test may play the role in the modulatory effects of non-competitive or glycine$_B$ site antagonists on morphine antinociception. For example, Zhu et al. [35] indicated an increase in expression of the NR1 mRNA in the thalamus and nucleus raphe magnus and a decrease in the spinal cord dorsal horn in morphine tolerant rats. Those changes were prevented by co-administration of the competitive NMDA receptor antagonist, LY 274614. The NR1 mRNA levels were unchanged in other regions involved in antinociception (e.g. PAG). These data suggest that various regions of the central nervous system and various subunits of NMDA receptor are associated with the development of tolerance to morphine antinociceptive effect, which can explain the discrepancy in the influence of NMDA antagonists on the development of morphine tolerance.

Another of the alternative explanations of our findings is that NMDA receptors are involved in the neuronal plasticity leading to the change in the responsiveness to the drug that occurs with chronic opiate administration (for review see [31]). The development of drug tolerance phenomenon represents a neuronal plastic changes and thus resembles learning processes [28]. NMDA receptor antagonists interfere with learning processes (for review see [9]) and it is possible that most of competitive and non-competitive NMDA receptor antagonists might attenuate the development of morphine tolerance through the inhibition of neuronal plasticity. As NMDA receptors contain a few binding sites, it seems to be possible that glycine$_B$ sites are not closely connected with learning processes and the influence of glycine$_B$ site antagonists on the development of morphine tolerance is not so crucial.

In my previous studies [18], the attenuation of morphine withdrawal syndrome (wet dog shakes) and development of morphine dependence in rats after administration of L-701.324 were observed. Thus, this results support the data obtained by Belozertseva et al. [2] in mice that another glycine$_B$ site antagonist, MRZ 2/576 suppresses several symptoms (jumping, shaking, forelimb tremor) of both naloxone-facilitated and spontaneous morphine withdrawal. It was also shown that naloxone-precipitated morphine withdrawal was attenuated in rats pretreated with partial agonists/non-

selective antagonists of glycine$_B$ receptor [17, 27] or full glycine$_B$ site antagonist, e.g. ACEA-1021 [26].

The literature data and present results indicate that the blockade of glycine$_B$ sites suppresses the morphine withdrawal syndrome (wet dog shakes or jumping) or the development of morphine dependence, but the involvement of these sites in the development of tolerance to morphine antinociceptive effect plays a lesser role, and is dependent on the test, time of administration or strain of animals. However, on the basis of the above-described experiments, it can be assumed that different brain structures or neuronal mechanisms are involved in the development of morphine dependence and tolerance.

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