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M-cholinoblockers with central action and naloxone: antinociceptive properties and interaction in the hot plate test on mice

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The literature contains contraversial information about the effect of M-cholinoblockers on pain sensitivity. The use of plants that contain cholinolytic tropane alkaloids for analgesic purposes has been known since ancient Rome. For example, Pliny the Elder in Naturalis Historia wrote about using the juice of mandrake or black henbane before surgical procedures for pain relief, and Galen used mandrake roots or henbane seeds to ease toothache [1]. Today, these remedies can be considered one group of adjuvant analgesics, but this effect has not been studied enough. The peak of publications on this topic was in the 1970s–1990s, which explains the need to cite many studies from that period.

In study [1], it was reported that in the hot plate test atropine sulfate has different effects on pain sensitivity: in very low (0.001–0.01 mg/kg) and relatively low (0.1 mg/kg) doses it produces a central antinociceptive effect; at a dose of 1 mg/kg it has no effect, and at high doses (5 mg/kg) it increases pain sensitivity. However, early studies [2] showed that atropine (1 mg/kg) lowers the pain threshold in rodents. Thus, the results of different studies on the effect of M-cholinoblockers on pain sensitivity are contradictory, and the reason for the complex dose-dependent effect remains unclear. More recent publications [3] report that atropine and scopolamine in the hot plate test increase the latency time (LT) of a nociceptive reaction in a dose-dependent way if hind paw licking is used as a criterion, and do not increase it when other behavioral reactions (jumping, etc.) are used.

The mechanism of the analgesic effect of these substances is associated with the blockade of presynaptic M-cholinoreceptors. The antagonism of pirenzepine, dicyclomine, and oxotremorine toward atropine-induced analgesia indicates the participation of M1-type cholinoreceptors in this mechanism. Possible interaction between the cholinergic and opioid systems is also not excluded. The instructions for atropine sulfate state that it reduces the analgesic effect of opiates [4]. But in study [2], naloxone causes hyperalgesia in rodents, which atropine (1 mg/kg) enhances. On the other hand, some publications report analgesic properties of naloxone [5].

Therefore, it is reasonable to verify the dose-dependent effect of several M-cholinoblockers on pain sensitivity, clarify the similar properties of naloxone, and assess the interaction between these agents.

The aim of the study – to determine the effect of atropine sulfate, scopolamine hydrobromide, and platyphylline hydrotartrate over a wide

range of doses, as well as naloxone, on pain sensitivity in mice in the hot plate test; and to identify the type of interaction between antagonists of M-cholinoreceptors and opioid receptors in their influence on nociception.

Materials and methods. The study was carried out at the Educational and Scientific Institute of Applied Pharmacy of the National Pharmaceutical University (NUPh) on 117 adult male white mice weighing 30–40 g. All studies were carried out in compliance with bioethical standards in accordance with the Law of Ukraine and European Convention for the protection of vertebrate animals used for experimental and other scientific purposes (Strasbourg, 1986) [6].

A model of somatic pain was used and reproduced in the hot plate test (Hot/Cold Plate device, Bioseb, USA) at a surface temperature of 53 °C. The nociceptive reaction was evaluated by the LT of hind paw licking, which is considered the most accurate marker of pain sensitivity [3]. Additional behavioral patterns were also recorded – licking of the front paw and jumping. If no nociceptive reaction was observed by the 60th second, the mouse was removed from the plate to prevent burns; in such cases the latency time was assumed to be 60 s.

Two experimental series were performed. In the first series, the effect of the centrally acting M-cholinoblocker scopolamine on pain sensitivity was examined. The mice were randomly divided into 2 groups. Group 1 – control (n = 24): animals received an intraperitoneal (i.p.) injection of 0.9% NaCl solution at a volume of 0.1 ml/10 g. Mice in group 2 (n = 19) received i.p. injections of scopolamine hydrobromide trihydrate (Thermo Fisher Scientific, China) at a dose of 1.5 mg/kg in the same volume. The LT of the nociceptive reaction was measured 30 min after injection. The large number of observations was necessary to reliably detect the effect on nociception at the level close to the standard deviation of LT.

In the second experimental series, the effects of different doses of three M-cholinoreceptor antagonists, as well as the opioid receptor antagonist naloxone and its combination with scopolamine, on pain sensitivity were assessed. The protocol of this experiment differed from the previous one in that it included measuring LT at baseline and after administration of the tested substances. The animals were randomized into 9 groups, and experiments were conducted on different days. Group 1 – control: mice received i.p. 0.9% NaCl (n = 26; all control animals were combined into one group because their results from different days were similar). Mice in groups 2–4 received i.p. atropine sulfate solution (Darnytsia, Ukraine) at doses of 0.1 mg/kg (group 2, n = 7), 1 mg/kg (group 3, n = 6), and 5 mg/kg (group 4, n = 6). The high dose of 5 mg/kg was used because it has been reported [1] to increase pain sensitivity in the hot plate test. Mice in groups 5–6 received i.p. platyphylline hydrotartrate (LLC "Pharmaceutical Company "Zdorovye") at doses of 0.125 mg/kg (group 5, n = 6) and 1.25 mg/kg (group 6, n = 6). Animals in groups 7–8 received scopolamine hydrobromide at doses of 0.1 mg/kg (group 7, n = 6) and 1.0 mg/kg (group 8, n = 6). These doses of platyphylline hydrotartrate and scopolamine were equimolar to atropine sulfate doses of 0.1 mg/kg and 1 mg/kg. Higher doses of these agents were not used, in particular due to the dose-dependent increase in locomotor activity and anxiety caused by scopolamine at doses of 3 mg/kg and 10 mg/kg [7] (these manifestations may interfere with

the behavioral phenomena considered in the hot plate test), and for bioethical reasons to reduce the number of animals in the study. LT was measured 30 min after administration of the M-cholinoblockers. Mice in group 9 (n = 5) received i.p. naloxone (Naloxone-ZN, LLC "Zdorovya Narodu", Ukraine) at a dose of 5 mg/kg [8, 9]; LT was measured after 30 min, then scopolamine hydrobromide (1 mg/kg) was administered, and the LT was measured again after 30 min. Based on the pharmacokinetic parameters of scopolamine in rodents [10], this protocol is appropriate for the purpose of the study. The observation time is due to the fact that within 30 min naloxone exhibits neurotropic effects in mice [11].

For statistical processing (Statistica 12.0), the Mann-Whitney U test was used for between-group comparisons, and the Wilcoxon signed-rank test was used to assess changes within groups (before vs. after). The frequency of certain effects in groups was compared using Fisher's angular transformation (φ-test). To determine sample size in the initial scopolamine experiment, the effect size (D) was used. The value of D depends on the expected difference between mean values relative to the standard deviation and equals the desired difference in means divided by the standard deviation (D = required difference in means / standard deviation). Based on this, to detect a statistically significant difference between the control and experimental groups at the level of one standard deviation, D must equal 1. For D = 1, the required sample size is 23 [12]. In later experiments, the sample size was reduced for bioethical reasons and due to the high sensitivity of the method. The results are presented as M ± m and Me [Q25; Q75]. Differences were considered statistically significant at $p < 0.05$.

Results and discussion. In the first series of experiments, as shown in Table 1, scopolamine at a dose of 1.5 mg/kg produced a clear analgesic effect, increasing the latency time of the nociceptive reaction by an average of 157% ($p < 0.01$). This provided grounds to proceed to the second series in order to determine the influence of other M-cholinoreceptor antagonists on nociception and the dose-dependence of this effect.

As shown in Table 2, the mean baseline LT for hind paw licking in the

Table 1

Effect of scopolamine hydrobromide (1.5 mg/kg) on the nociceptive response of mice in the hot plate test (M ± m, Me [Q25; Q75])

Group, number of animals	Latency to hind-paw licking, s		Change relative to control, %
Control, n = 24	M ± m	14.0 ± 1.0	–
	Me [Q25; Q75]	13.05 [10.08; 16.38]	
Scopolamine hydrobromide, n = 19	M ± m	36.02 ± 4.17**	+ 157
	Me [Q25; Q75]	30.0 [22.20; 60.0]**	

*Note. Statistically significant differences compared to the control: **p < 0.01 (according to the Mann-Whitney criterion).*

control group was (21.93 ± 2.11) s, and after repeated measurement 30 min later it did not change significantly: it showed only a tendency to increase by 16.4%, which was not statistically significant according to the Wilcoxon paired test.

A slight increase in LT was observed only in 50% of the animals, while in the other 50% the LT slightly decreased. This means that mice do not develop habituation to repeated testing on the hot plate, and it confirms that reliable results on the effects of the studied substances on pain sensitivity can be obtained. Our results agree with the data in [13], which show that repeated testing does not cause significant changes in pain sensitivity in rodents.

It should be noted that other behavioral patterns of the mice were unstable. For example, licking of the front paws, even during the first testing in the baseline state, was not observed in all animals and varied greatly: the number of such licking events per animal in different groups ranged from (0.17 ± 0.17) (observed only in 1 out of 6 mice) to (3.60 ± 1.21) (the difference was significant at $p < 0.01$). When this behavior occurred, it happened either before or after hind paw licking, meaning it did not have a regular time pattern. This corresponds to the data in [3], which indicate that front paw licking is not a reliable criterion of nociceptive reaction in the hot plate test.

As shown in Table 2, in the atropine sulfate group at a dose of 0.1 mg/kg, a moderate increase in LT for hind paw licking was observed in 71.4% of cases and showed only a tendency to increase (on average by 17.6% compared to baseline). At a dose of 1 mg/kg, this effect occurred in 50% of cases (an increase of 40%). With a large increase in dose to 5 mg/kg, the LT increase was statistically significant compared to the control group ($p < 0.05$), occurred in 100% of the animals, and reached 108% relative to baseline ($p < 0.05$). Other behavioral patterns (front paw licking, jumping as an escape attempt) were unstable, appeared only in some animals, sometimes repeated and sometimes did not, or appeared for the first time during the second test 30 min after injection. When this response repeated after the administration of an M-cholinoblocker, it usually occurred at a similar or later time than during the baseline test. Front paw licking was more common during the baseline test but not during the final test, and in some cases it appeared as grooming behavior – a sign of restlessness. Thus, using jumping and front paw licking as stable and reliable criteria for nociceptive reaction in studies of M-cholinoblockers appears inappropriate.

Platyphylline hydrotartrate caused a statistically significant increase in LT compared to baseline ($p < 0.05$) at both doses – by 124.3% at 0.125 mg/kg, and by 72.5% at 1.25 mg/kg (Table 2).

Scopolamine hydrobromide, similarly to the testing at 1.5 mg/kg, caused a statistically significant ($p < 0.05$) analgesic effect at both lower doses: LT increased by 89.4% at 0.1 mg/kg and by 82.1% at 1 mg/kg (Table 2). A characteristic feature of mouse behavior under the effect of this M-cholinoreceptor antagonist was a significant increase in the number of rearing events on the hind legs: up to (4.50 ± 0.92) at a dose of 0.1 mg/kg compared to (2.15 ± 0.50) in the intact control ($p < 0.05$), and up to (5.67 ± 2.55) at a dose of 1 mg/kg. This behavior is a marker of escape attempts and anxiety in rodents in the hot plate test [14].

Table 2

Effect of M-cholinoblockers and naloxone on the nociceptive response of mice in the hot plate test over time (M ± m, Me [Q25; Q75])

Dose, mg/kg; n	Latency to hind-paw licking, s		change, %	Number of animals with increased latency, abs./%
	baseline	after 30 (60[@]) min		
Intact control				
n = 26	21.93 ± 2.11 18.20 [15.43; 27.53]	25.53 ± 3.24 20.95 [15.20; 25.23]	+ 16.4	13/50
Atropine sulfate				
0.1, n = 7	18.74 ± 1.99 17.80 [14.60; 21.80]	22.04 ± 2.02 22.0 [19.30; 24.30]	+ 17.6	5/71.4
1.0, n = 6	27.77 ± 3.55 25.65 [23.15; 26.43]	38.88 ± 7.51 37.25 [26.83; 54.50]	+ 40.0	3/50
5.0, n = 6	21.55 ± 3.07 19.60 [17.15; 23.25]	44.82 ± 7.33 50.70 [30.53; 60.0]*,#	+ 108.0	6/100^^
Platyphylline hydrotartrate				
0.125, n = 6	12.25 ± 2.14 10.80 [9.78; 12.73]**	27.48 ± 6.76 23.55 [21.75; 24.23]#	+ 124.3	6/100 ^^
1.25, n = 6	12.93 ± 1.33 12.85 [10.68; 14.73]**	22.30 ± 2.30 21.55 [19.65; 25.48]#	+ 72.5	5/83.3
Scopolamine hydrobromide				
0.1, n = 6	15.07 ± 3.70 11.70 [9.45; 16.50]	28.55 ± 6.55 23.60 [21.93; 27.15]#	+ 89.4	6/100^^
1.0, n = 6	22.77 ± 3.96 19.85 [15.53; 28.45]	41.47 ± 6.61 39.35 [30.43; 56.00]*,#	+ 82.1	5/83.3
Naloxone				
5.0, n = 5	25.52 ± 5.68 17.40 [17.00; 36.80]	35.76 ± 7.05 31.20 [29.60;40.30]#	+ 40.1	100^^
Naloxone + scopolamine hydrobromide				
5.0 + 1.0, n = 5	25.52 ± 5.68 17.40 [17.00; 36.80]	55.84 ± 4.16@ 60.0 [60.0; 60.0]**,#	+ 118.8	100^^

*Note. Statistically significant differences compared to the control: *p < 0.05, **p < 0.01 (according to the Mann-Whitney criterion); ^^p < 0.01 (according to Fisher's angular transformation); with the initial state within the group: #p < 0.05 (even Wilcoxon criterion); n – number of animals in the group, @after 60 min.*

Naloxone showed analgesic activity: it significantly increased the LT of the nociceptive reaction (on average by 40.1%, $p < 0.05$) in all animals (Table 2). Scopolamine (1 mg/kg), when administered to these mice under

naloxone action, caused a further increase in the analgesic effect – LT increased in all animals (on average by 118.8% relative to baseline, $p < 0.05$). Thus, under opioid receptor blockade, the analgesic effect of the M-cholinoreceptor antagonist is potentiated. It should be noted that after scopolamine administration following naloxone, the number of jumps on the hot plate as escape behavior increased significantly (on average to (8.0 ± 2.66) compared to (2.46 ± 1.28) in the intact control, $p < 0.05$, and (1.60 ± 0.60) under naloxone *per se*, $p < 0.05$). As the latter value shows, the intensity of this pattern in the naloxone *per se* group was low and even lower than the control level, which does not correspond to the data in [15], where rodents under naloxone tend to react in the hot plate test mainly with escape behavior.

Thus, all tested M-cholinoreceptor antagonists produced an analgesic effect. Scopolamine and platyphylline showed clear analgesic properties at low doses (0.1–0.125 mg/kg). Atropine, at the lowest tested dose of 0.1 mg/kg, showed only a tendency to reduce pain sensitivity, but this effect increased with the dose and reached its maximum at 5 mg/kg. Therefore, atropine sulfate demonstrates a dose-dependent analgesic action that progressively increases across a wide dose range. These results contradict the data in [1], according to which the analgesic effect of atropine sulfate was observed only at doses of 0.001–0.01 mg/kg, and higher doses produced the opposite effect. The differences may be related to methodological features of the cited study, where the criterion of the nociceptive reaction was licking of any limb – both front and hind. This approach, according to our observations and the data in [3], gives less accurate results than the latency time of hind paw licking. Another possible reason for the differences may be a pharmacogenetic factor: the cited study used Swiss mice, whereas our study used random-bred animals.

The effect of naloxone on pain sensitivity is complex. At ultralow doses (1–100 ng/kg), naloxone blocks mainly high-affinity opioid receptors associated with Gs-proteins, which strongly enhances the antinociceptive activity of morphine and at the same time reduces opioid tolerance and dependence [16]. Analgesia caused by low doses of naloxone is considered paradoxical; it was observed after systemic administration of naloxone *per se* or in combination with opioid drugs and was confirmed *in vivo* and *in vitro* in a trigeminal nociception model after local administration into vibrissae in the orofacial formalin test in rats [17]. Non-opioid mechanisms of naloxone are also discussed: at low doses it inhibits toll-like TLR4 receptors in microglia, which play an important role in glial dysregulation of opioidergic mechanisms. This effect of naloxone prevents the release of pro-inflammatory cytokines, which reduces pain sensitivity in a model of neuropathic pain [18].

We used a higher dose of naloxone (5 mg/kg), for which an analgesic effect has been described due to blocking the inhibitory influence of μ-opioid receptors on dynorphinergic neurons, leading to an increase in endogenous opioids and their agonistic action on κ-opioid receptors, to which naloxone has lower affinity [5]. A similar mechanism of naloxone's analgesic action at 10 mg/kg in a model of chronic inflammatory pain induced by Freund's adjuvant was described in [19]. However, in a stress model induced by forced walking for 6 or 9 days, naloxone (10 mg/kg) reduced stress-

induced antinociception, meaning it showed pronociceptive properties. There are also other reports of naloxone-induced hyperalgesia in rodents and its enhancement by atropine [2]. In study [1], naloxone (1 mg/kg) did not affect pain sensitivity in the hot plate test and did not influence the antinociceptive effect of atropine compared to atropine alone. Our results in the model of nociceptive pain ("Hot Plate") confirm the presence of clear analgesic properties of naloxone at the moderately high dose of 5 mg/kg and the enhancement of antinociceptive action in the combination of naloxone with scopolamine.

Future research should focus on studying the effect on pain sensitivity of a wider range of M-cholinoreceptor antagonists with both central and peripheral action and with different selectivity profiles, further clarification of the mechanisms and dose-dependence of the antinociceptive effects of M-cholinoblockers and naloxone, and evaluation of interactions between M-cholinoblockers and analgesics of different pharmacological groups.

Conclusions

1. All three studied M-cholinoreceptor antagonists (atropine sulfate, scopolamine hydrobromide, platyphylline hydrotartrate) show analgesic properties in the somatic pain model using the hot plate test in mice.
2. According to the increase in the latency of hind-paw licking, the effect of atropine becomes stronger across a wide range of tested doses (a slight tendency at 0.1 mg/kg and 1 mg/kg, and a significant effect at 5 mg/kg). Scopolamine causes a similarly strong analgesia at both 0.1 and 1 mg/kg. Platyphylline shows a stronger effect at 0.125 mg/kg (equimolar to 0.1 mg/kg of atropine) and a weaker effect at 1.25 mg/kg (equimolar to 1 mg/kg of atropine). Scopolamine at a higher dose of 1.5 mg/kg causes a more pronounced analgesic effect compared to the synchronous control.
3. The opioid receptor antagonist naloxone (5 mg/kg) shows a moderate antinociceptive effect, which becomes much stronger when M-cholinoreceptors are blocked by scopolamine (1 mg/kg).
4. Behavioral patterns such as licking of the front paws, jumping, and vertical standing, unlike licking of the hind paws, are not stable or reliable markers of nociceptive reaction in the hot plate test.

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Подяка. Автори висловлюють глибоку вдячність усім захисникам України, завдяки яким це дослідження стало можливим.

Конфлікт інтересів. Автори заявляють про відсутність конфлікту інтересів.

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M-cholinoblockers with central action and naloxone: antinociceptive properties and interaction in the hot plate test on mice

Centrally acting M-cholinoreceptor antagonists are usually described as drugs that affect autonomic functions. However, their possible analgesic properties are still not well studied, even though tropane alkaloids were historically used for pain relief. Modern publications show contradictory results about the effect of atropine and scopolamine on pain sensitivity, and some authors discuss the role of cholinergic and opioid mechanisms in their antinociceptive action.

The aim of the study – to determine the effect of atropine sulfate, scopolamine hydrobromide, and platyphylline hydrotartrate over a wide range of doses, as well as naloxone, on pain sensitivity in mice in the hot plate test; and to identify the type of interaction between antagonists of M-cholinoreceptors and opioid receptors in their influence on nociception.

The study used 117 adult male outbred white mice. In the hot plate test at 53 °C, the latency of the nociceptive reaction was measured (licking of the hind paw and other behavioral patterns such as jumps, licking of the front paws, and vertical standing) 30 min after drug administration. In the first series, the effect of scopolamine hydrobromide trihydrate (1.5 mg/kg, intraperitoneally) was evaluated. In the second series, atropine sulfate (0.1, 1, 5 mg/kg), platyphylline hydrotartrate (0.125 mg/kg and 1.25 mg/kg, equimolar to 0.1 and 1 mg/kg of atropine sulfate), scopolamine hydrobromide trihydrate (0.1 mg/kg and 1 mg/kg), and naloxone (5 mg/kg) were used alone and in combination with scopolamine (1 mg/kg).

The instability of additional behavioral patterns confirmed that hind-paw licking is the most reliable nociceptive marker under the action of M-cholinoblockers. All studied M-cholinoblockers were able to reduce pain sensitivity. Atropine sulfate showed a dose-dependent effect: from a slight increase of latency

at low doses to a strong and statistically significant analgesia at 5 mg/kg. Scopolamine and platyphylline showed strong analgesic effects already at low doses (0.1–0.125 mg/kg). Naloxone (5 mg/kg) produced a moderate but statistically significant antinociceptive effect. When naloxone was combined with scopolamine, the latency time more than doubled compared to baseline, showing a strong enhancement of effects and a complex interaction between cholinergic and opioid systems.

The results show that M-cholinoblockers may have potential as adjuvant analgesics and highlight the importance of studying their interaction with the opioid system. This may help in developing new combined pharmacological approaches for pain treatment.

Key words: M-cholinoblockers, atropine, scopolamine, platyphylline, naloxone, pain sensitivity, hot plate test, mice

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М-холіноблокатори з центральним компонентом дії та налоксон: синергічні антиноцицептивні властивості в тесті «гаряча пластина» у мишей

Антагоністи М-холінорецепторів з центральною дією традиційно розглядаються переважно як засоби, що впливають на вегетативні функції, однак їхні потенційні аналгетичні властивості залишаються недостатньо вивченими, незважаючи на численні історичні згадки про застосування тропанових алкалоїдів з метою знеболення. У сучасних публікаціях наявні суперечливі результати щодо впливу атропіну й скополаміну на больову чутливість, повідомляється про можливу участь холінергічних та опіоїдергічних механізмів у їхній антиноцицептивній дії.

Мета дослідження – з'ясувати вплив атропіну сульфату, скополаміну гідробромід, платифіліну гідротатрату в широкому діапазоні доз, а також налоксону на больову чутливість мишей у тесті «Гаряча пластина»; визначити характер взаємодії між антагоністами М-холінорецепторів та опіоїдних рецепторів за впливом на ноцицепцію.

У дослідженні використано 117 безпородних дорослих білих мишей-самців. У тесті «Гаряча пластина» за температури 53 ˚С визначали латентний час ноцицептивної реакції (облизування задньої лапи та інші поведінкові патерни – стрибки, облизування передніх лап, вертикальні стійки) через 30 хв після введення досліджуваних засобів. У 1 серії експериментів оцінювали вплив скополаміну гідробромід тригідрату (1,5 мг/кг внутрішньоочеревинно). У 2 серії використовували атропіну сульфат (0,1; 1; 5 мг/кг), платифіліну гідротартрат (0,125 мг/кг та 1,25 мг/кг, що еквімолярно 0,1 та 1 мг/кг атропіну сульфату), скополаміну гідробромід тригідрат (0,1 мг/кг та 1 мг/кг), а також налоксон (5 мг/кг) *per se* та в комбінації зі скополаміном (1 мг/кг).

Нестійкість додаткових поведінкових патернів підтверджує, що саме облизування задньої лапи може розглядатись як найнадійніший критерій ноцицептивної реакції в умовах дії М-холіноблокаторів. Усі досліджені М-холіноблокатори здатні знижувати больову чутливість. Атропіну сульфат продемонстрував дозозалежний характер дії: від тенденційного збільшення латентного часу облизування задньої лапи в низьких дозах до значної статистично значущої аналгезії за дози 5 мг/кг. Скополамін і платифілін, навпаки, виявили сильний аналгетичний ефект уже в низьких дозах (0,1–0,125 мг/кг). Налоксон (5 мг/кг) виявив помірні, але статистично значущі антиноцицептивні властивості. За поєднання налоксону зі скополаміном латентний час больової реакції збільшувався більш ніж удвічі щодо вихідного показника, що свідчить про значне посилення ефектів і складну взаємодію між холінергічною та опіоїдергічною системами.

Отримані результати свідчать про перспективність подальшого вивчення М-холіноблокаторів як потенційних ад'ювантних аналгетиків, а також механізмів їхньої взаємодії з опіоїдергічною системою, що може мати значення для розробки нових комбінованих підходів до фармакологічної корекції больових синдромів.

Ключові слова: М-холіноблокатори, атропін, скополамін, платифілін, налоксон, больова чутливість, тест «Гаряча пластина», миші

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