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ORIGINAL ARTICLE

Preclinical evidence for the antihyperalgesic activity of CDP-choline in oxaliplatin-induced neuropathic pain

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Summary

Purpose: *This study was designed to evaluate the antihyperalgesic effect of CDP-choline (cytidine-5'-diphosphate-choline; citicoline) in a rat model of neuropathic pain produced by oxaliplatin (OXA).*

Methods: *A single administration of OXA (6 mg/kg intraperitoneally/ip) was used for induction of neuropathy. We assessed the antihyperalgesic effect of intracerebroventricularly (icv) administered CDP-choline (0.5, 1.0 and 2.0 μmol) using the rat paw pressure test (Randall-Selitto).*

Results: *CDP-choline significantly reduced OXA-induced mechanical hyperalgesia, in a dose- and time-dependent manner. The antihyperalgesic effect of CDP-choline was blocked by the neuronal high affinity choline uptake inhibitor hemicholinium-3 (1 μg; icv), the nonselective nicotinic receptor antagonist mecamylamine (50 μg; icv), the α7 selective nicotinic acetylcholine receptor antagonist α-bungarotoxin (2 μg; icv), and the gamma-amino butyric acid (GABA)-B receptor antagonist CGP-35348 (20 μg; icv), but not by the nonselective opioid receptor antagonist naloxone (10 μg; icv) and the nonselective muscarinic receptor antagonist atropine (10 μg; icv).*

Conclusion: *These findings indicate that CDP-choline exerts an antihyperalgesic effect in OXA-induced neuropatic pain and it can be tested in clinical trials.*

Key words: *CDP-choline, neuropathy, oxaliplatin, pain*

Introduction

OXA is one of the most important cytotoxic drugs in the oncologist's armamentarium. It is a third-generation platinum compound and has become almost indispensable for the treatment of colorectal cancer [1]. Neurotoxicity is a well-known side effect of all the platinum compounds. However, unlike other platinum compounds, OXA causes an acute painful neuropathy which appears during or immediately after the infusion [2-4]. This form of neuropathy is encountered in about 90% of all patients exposed to OXA [2-4]. The patients also suffer from sensory symptoms in the form of distal or perioral paresthesias or dysesthesias triggered or aggravated by exposure to cold. Although mechanisms underlying this troublesome side effect still remain unclear, preclinical studies have suggested that OXA caused a transient channelopathies of axonal voltage-gated sodium and potassium channels [5-8]. It has also been postulated that OXA blocks neuron voltage-gated sodium channels via a chelation of calcium ions through the action of its metabolite, oxalate [9]. Currently, there is no satisfactory medical strategy for preventing or attenuating the painful neurotoxicity observed after OXA administration.

CDP-choline is an endogenously synthesized nucleotide, and an essential intermediate in the biosynthesis of structural phospholipids of cell membranes, especially phosphatidylcholine [10]. Following administration by both oral and parenteral routes, CDP-choline is hydrolyzed to cytidine and choline, which leads to increased plasma and tissue concentrations of these metabolites [10]. CDP-choline activates biosynthesis of structural phospholipids of neuronal membranes, increases brain metabolism, and acts upon the levels of dif-

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ferent neurotransmitters such as norepinephrine and dopamine. Owing to its peculiar pharmacological characteristics and the action mechanisms, CDP-choline has been considered as a potential candidate agent for the treatment of various types of neurological conditions like cerebral vascular disease, head trauma, and Alzheimer disease [11].

Recent preclinical studies in our laboratory indicate that *icv* administration of CDP-choline elicits dose- and time-dependent antinociceptive and antihyperalgesic effects in behavioral models of neuropathic and inflammatory pain in rats [12-14]. The findings obtained from these studies suggest that these effects of CDP-choline are probably mediated by an interaction with supraspinal alpha-7 nicotinic acetylcholine receptors (α7 nAChRs), gamma-amino butyric acid [GABA]-B receptors-, and/or opioid receptors [12-14]. Taken together, these data led us to hypothesize that CDP-choline may also have antinociceptive effects on OXA-induced painful neuropathy. Therefore, the present study was designed to investigate the antihyperalgesic potential of CDP-choline in a rat model of neuropathic pain produced by a single administration of OXA. Moreover, efforts were also made to examine some of the mechanisms through which CDP-choline may exert its antihyperalgesic action, notably its possible interaction with cholinergic system.

Methods

Animals

Experiments were performed on 250- to 350-g adult male Sprague-Dawley rats (Experimental Animals Breeding and Research Center, Uludag University Faculty of Medicine, Bursa, Turkey). Animals were housed in standard laboratory conditions with *ad libitum* access to food and water at least one week before the experiments. All experiments were performed according to the Ethical Guidelines of the International Association for the Study of Pain [15] and all procedures were approved and monitored by the local institution's Ethics Committee.

Agents used in the study

OXA was provided by Sanofi-Aventis, Istanbul, Turkey. The following drugs were obtained from Sigma Chemical Co. (St. Louis, Missouri, USA): choline chloride, atropine sulfate, mecamylamine hydrochloride, hemicholinium-3 (HC-3), α-bungarotoxin (α-BgTx), and CGP-35348. CDP-choline and naloxone were purchased from Fluka Biochemicals Inc. (Buchs, Switzerland) and cytidine from Acros Organics (Geel, Belgium). All doses were calculated as the free base and drugs were dissolved in saline.

Intracerebroventricular injection procedure

The procedure of *icv* injection was carried out as previously described [12-14]. The rats were implanted with a guide cannula under ether anesthesia. Coordinates for the lateral cerebral ventricle were 1.5 mm lateral to the midline, 1.0 mm posterior to the bregma, and 4.5 mm ventral to the skull surface. According to these coordinates a 21-gauge stainless steel hypodermic tube guide cannula was lowered 4.2 mm below the surface of the skull and fixed to the skull with acrylic cement. After the surgical procedure, all animals were housed in individual metal cages and allowed to recover from anesthesia for 4-5 h. During this period, animals did not show any sign of pain or discomfort. *icv* injections were performed through a 25-gauge stainless steel injection cannula inserted through and extending 0.3 mm beyond the guide cannula. The drug injections were performed on the day following *icv* cannulation. The injection cannula was attached to a 50-µl Hamilton microsyringe with PE-50 tubing, which was filled with saline or saline containing the desired dose of the drug of interest in 10 µl of solution. Drugs injections lasted 30 s and the injection cannula was left in place for an additional 30 s to minimize flow of the drug solution back up the injector track. The volume for *icv* injection was 10 µl throughout the study and was monitored by observing the movement of a small air bubble within the tubing. At the end of the experiments, the correct location of the cannula into the lateral ventricle was verified by injecting 10 µl of diluted (1:10) India ink and their brains were examined macroscopically after sectioning.

Behavioral testing-Mechanical hyperalgesia

Mechanical hyperalgesia was defined as a decrease in the paw withdrawal threshold from baseline, and determined for left and right hind paws using the Randall-Selitto paw pressure technique as previously described [16]. Increasing pressure measured with an analgesimeter (Apelex; Ugo Basile, Comerio, Italy) was applied to the hind paws, with a cut-off at 250 g. The rats were trained in the nociceptive test daily for 2 days before the experiments to stabilize baseline responses. Each hind paw was tested 3 times with a 5-min inter-trial interval. All behavioral tests were conducted in a quiet, temperature-controlled (20 to 220C) room between 9:00 AM and 4:00 PM. Rats were habituated to the experimental procedures by handling for 4 days prior to the experiment.

Administration of test agents

To generate the model of OXA-induced neuropathic pain, OXA was dissolved in a 5% glucose solution and single dose of 6 mg/kg was administered *ip* to rats as described by Ling and co-workers [17,18]. The mechanical paw withdrawal thresholds were measured

immediately (0 min) and at 60, 120, 180, 240 min, and on days 1, 2, 3, 4, 7, 14 and 21 after administration of OXA.

All of the following experiments were performed on the second day after OXA injection:

CDP-choline (0.5, 1, and 2 µmol) or saline (10 µl) were injected *icv*, and mechanical paw withdrawal thresholds were measured at 15, 30, 45, 60, 90, and 120 min after the injections.

In order to determine whether the *icv* injected equimolar doses of choline and cytidine, immediate hydrolysis products of CDP-choline, could produce independent antinociceptive effects, 1 µmol CDP-choline, choline, cytidine or saline (10 µl) were injected to the rats. The mechanical paw withdrawal thresholds were measured at 15, 30, 45, 60, 90, and 120 min after the injections.

In another set of experiments, atropine (nonselective muscarinic cholinergic receptor antagonist; 10 µg), mecamylamine (nonselective nicotinic cholinergic receptor antagonist; 50 µg), α-BgTx (selective α7nAChR antagonist; 2 µg), HC-3 (specific inhibitor of high-affinity neuronal choline uptake; 1 µg), naloxone (nonselective opioid receptor antagonist; 10 µg), CGP-35348 (selective $GABA_B$ receptor antagonist; 20 µg), or saline (10 µl) were injected *icv* 15 min before CDP-choline (1 µmol; *icv*) or saline (10 µl; *icv*) injections. The mechanical paw thresholds were measured at 15, 30, 45, and 60 min after CDP-choline or saline injections. The doses and administration schedules of the above-mentioned antagonists were selected from studies demonstrating the prevention of antinociceptive effects induced by the corresponding agonists [12-14].

Statistics

All data were expressed as the mean ± standard error of the mean (S.E.M). Data were analyzed using one-way or two-way analysis of variance (ANOVA) followed by the Student-Newman-Keuls test. A p-value of less than 0.05 was considered as significant.

Results

Effects of OXA on mechanical nociceptive threshold

Before OXA infusion on day 0, the paw withdrawal thresholds of the rats in response to mechanical pressure were 144.3 ± 2.5 g. No significant changes in the paw withdrawal thresholds were detected over the entire 240-min observation period following OXA injection (data not shown). The paw withdrawal thresholds significantly decreased on day 1 (66 ± 2 g; p<0.001), reached peak on day 2 (47.5 ± 1 g; p<0.001), remained lower than baseline at day 14 (128 ± 4 g; p=0.006), and returned to the pretreatment levels by day 21 (Figure 1).

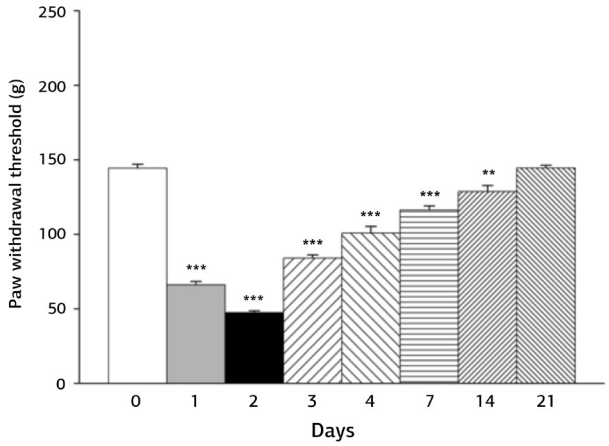

Figure 1. Time course of oxaliplatin (6 mg/kg *ip*) induced mechanical hyperalgesia. Results are expresses as mean ± SEM. The paw withdrawal thresholds to mechanical pressure started to decrease on day 1, peaked on day 2, and remained lower than baseline until day 14. (**p<0.01, ***p<0.001).

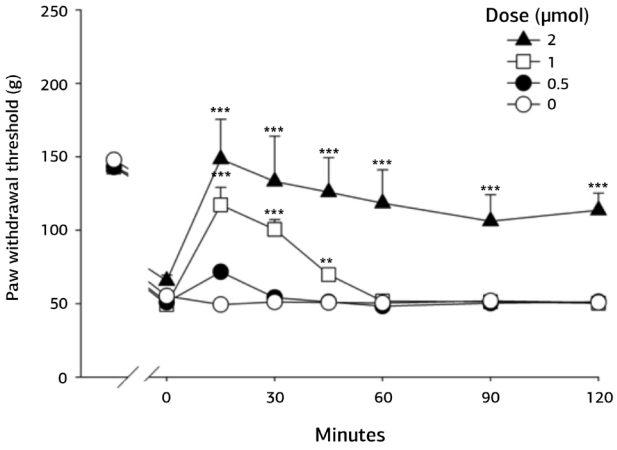

Figure 2. Effect of *ivc* injected CDP-choline (0.5, 1, and 2 µmol) or saline (10 µl) on paw withdrawal threshold in oxaliplatin-induced mechanical hyperalgesia. Results are expressed as mean ± SEM. **p<0.01 and ***p<0.001, significantly different from the values observed in the saline group.

Antihyperalgesic effect of CDP-choline on mechanical nociceptive threshold after central administration

Administration of CDP-choline (0.5, 1, and 2 µmol; *icv*) significantly attenuated OXA-induced decrease in the nociceptive threshold for mechanical hyperalgesia in a dose- and time-dependent manner (Figure 2). The antihyperalgesic effect of CDP-choline reached its maximum level at 15 min after its administration, and returned to pre-injection level within 60 min after injection of low-doses (0.5 and 1 µmol) of CDP-choline. The increase

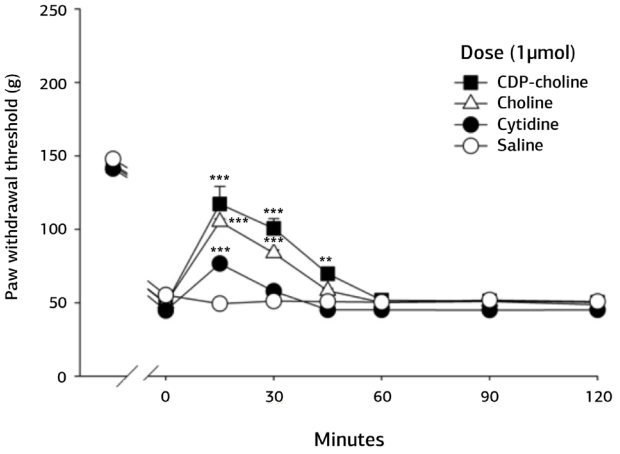

Figure 3. Effect of intracerebroventricularly injected equimolar doses of CDP-choline (1 µmol), choline (1 µmol), or cytidine (1 µmol) on paw withdrawal threshold in oxaliplatin-induced mechanical hyperalgesia. Results are expressed as mean ± SEM. **p<0.01 and ***p<0.001, significantly different from the values observed in the saline group.

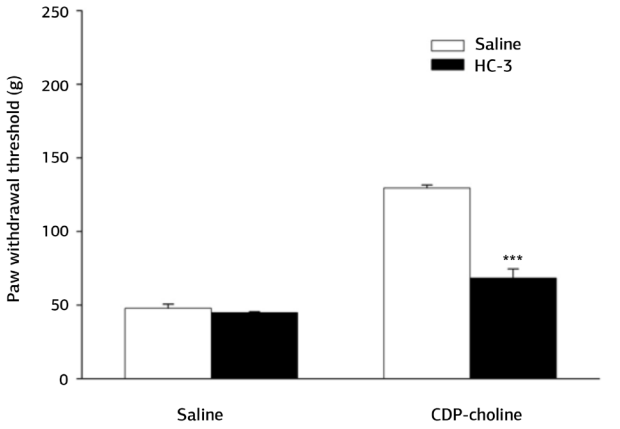

Figure 4. Effects of hemicholinium-3 (HC-3) pretreatment on the increase in paw withdrawal threshold induced by CDP-choline in oxaliplatin-induced mechanical hyperalgesia. Rats were pretreated with saline (10 µl *icv*) or HC-3 (1 µg *icv*) 15 min before *icv* administration of saline (10 µl) or CDP-choline (1 µmol). Results are expressed as mean ± SEM. ***p<0.001, significantly different from the values observed in the saline group.

in the withdrawal threshold after the highest dose of CDP-choline (2 µmol) was much greater and longer lasting than lower doses (Figure 2). The dose of 1 µmol of CDP-choline was selected for further experiments.

Antihyperalgesic effect of equimolar doses of choline and cytidine on the mechanical nociceptive threshold

Both choline (1 µmol; *icv*) and cytidine (1 µmol; *icv*) led to a significant increase in paw withdrawal threshold 15 min after their injection (p<0.001; Figure 3). However, choline showed a relatively more prominent and longer-lasting antihyperalgesic effect than cytidine.

Antagonism of the antihyperalgesic effect of icv CDP-choline

In order to explore whether the antihyperalgesic effect produced by *icv* injected CDP-choline was due to increased presynaptic cholinergic mechanisms, the rats were pretreated with HC-3 (1 µg; *icv*). HC-3 greatly reduced the CDP-choline (1 µmol; *icv*) antihyperalgesic action (p<0.001). HC-3 pretreatment alone had no effect on mechanical nociceptive threshold (Figure 4).

To further explore the involvement of receptors, various agents were evaluated for their ability to alter the antihyperalgesic effect of CDP-choline on neuropathic pain induced by OXA (Figures 5 and 6). Mecamylamine (50 µg; *icv*), α-BgTx (2 µg; *icv*), and CGP-35348 (20 µg; *icv*) significantly blocked the antihyperalgesic effect of CDP-choline (1 µmol;i.c.v) (p<0.001). In contrast, atropine (10 µg; *icv*) and naloxone (10 µg; *icv*) had no effect. None of these antagonists produced antihyperalgesic effect when tested alone.

Discussion

Because of its unique characteristics, OXA-induced neuropathy has become one of the most attractive research topics in recent years. Previous studies in animal models have largely focused on the OXA-induced chronic painful neuropathy; however, OXA-induced acute neuropathy has not been well-characterized [17]. In the present study, rats received a single injection of OXA (6 mg/kg; ip) for induction of acute neuropathic pain. This rat model of OXA-induced acute neuropathic pain was originally developed by Ling and colleagues [17, 18]. The peripheral neuropathy caused by chemotherapeutic agents has been widely evaluated experimentally in animals as hypersensitivity to mechanical stimuli and thermal stimuli in terms of mechanical allodynia/hyperalgesia and thermal allodynia/hyperalgesia [19,20]. In the study by Ling and colleagues [17], a single *ip* injection of OXA caused significant allodynia and hyperalgesia in response to cold stimuli (tail-immersion test) from 24 h to day 5, and mechanical allodynia (von Frey test) from day 3 to day 8. However, in contrast to our results, they did not observe any significant effect of the OXA treatment on mechanical hyperalgesia (Randall-Sellito test). In our study, as shown in Figure 1, mechanical hyper-

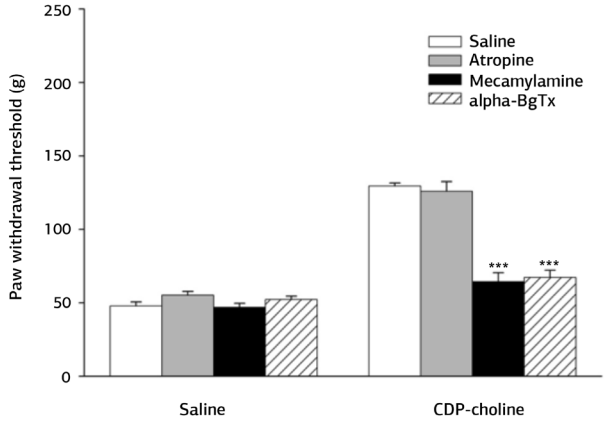

Figure 5. Effects of atropine, mecamylamine, and α-bungarotoxin (α-BgTx) pretreatments on the increase in paw withdrawal threshold induced by CDP-choline in oxaliplatin-induced mechanical hyperalgesia. Rats were pretreated with saline (10 μl *icv*), atropine (10 μg *icv*), mecamylamine (50 μg *icv*), or α-BgTx (2 μg *icv*), 15 min before *icv* administration of saline (10 μl) or CDP-choline (1 μmol). Results are expressed as mean ± SEM. ***p<0.001 significantly different from the values observed in the saline group.

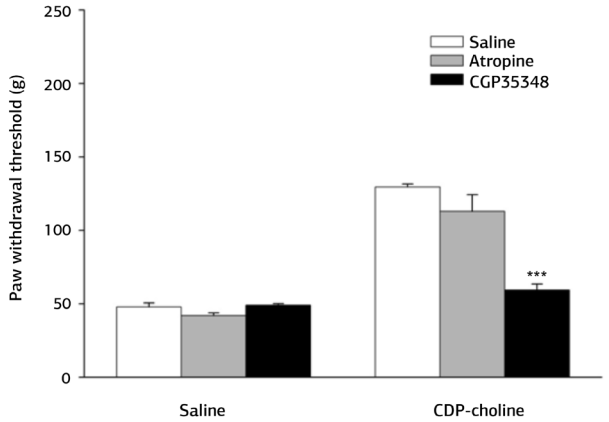

Figure 6. Effects of naloxone and CGP-35348 pretreatments on the increase in paw withdrawal threshold induced by CDP-choline in oxaliplatin-induced mechanical hyperalgesia. Rats were pretreated with saline (10 μl *icv*), naloxone (10 μg *icv*), or CGP-35348 (20 μg *icv*) 15 min before *icv* administration of saline (10 μl) or CDP-choline (1 μmol). Results are expressed as mean ± SEM. ***p<0.001 significantly different from the values observed in the saline group.

algesia started on day 1 after OXA injection, reached its peak on day 2, and persisted for 14 days. The pattern of OXA-related neuropathic pain in the study showed a little discrepancy from that observed in patients treated with OXA [20, 21], especially in terms of onset and duration of hyperalgesia.

There are limited clinical and preclinical data on the use of drugs to prevent or treat painful symptoms of OXA-induced acute neuropathy. Using OXA-induced neuropathic rats subjected to the cold allodynia test, Ling et al. [18] showed a significant reversal of allodynia after *ip* injection of 2 mg/kg pregabalin, 3 mg/kg lidocaine, and 4 mg/kg morphine. Another interesting study performed by Kawashiri and coworkers showed that oral co-administration of L type calcium channel blockers (diltiazem, nifedipine, and ethosuximide) is able to inhibit OXA-induced cold hyperalgesia in rats [22].

To our knowledge, our study provides the first preclinical evidence that the central administration of CDP-choline attenuates the mechanical hyperalgesia caused by OXA administration. This antihyperalgesic effect of CDP-choline was dose and time-dependent in the paw pressure test and more pronounced following the highest dose (2 μmol; *icv*). Its main metabolites, choline (1 μmol; *icv*) and cytidine (1 μmol; *icv*), were also able to produce an antihyperalgesic action (Figure 2). Studies in animal models have demonstrated that pharmacological activation of nicotinic receptors that contain α7 subunits decreases nociceptive responses in acute and inflammatory pain [12-14,23-25]. Choline activates α7 nAChRs, and decreases hyperalgesia in the late phase of the formalin test, but not in hot plate or tail flick latency tests [23]. Our previous studies have suggested a role for α7 nAChRs in a carregeenan-induced inflammatory pain and a constriction injury model of neuropathic pain in rats [12]. *icv* and intrathecal administration of choline, a selective full agonist at α7 nAChRs, is antinociceptive in a variety of pain models [12-14,26]. The centrally administered choline had also, as expected, significant antinociceptive activity against OXA-induced neuropathic pain. On the other hand, the antinociceptive effect of cytidine and its potential mechanism have not yet been clarified. In this study, cytidine produced a clear but short-lived antihyperalgesic effect. This finding is consistent with our previous study which showed that centrally administered cytidine exerted and analgesic effect in acute pain models [13]. Further investigations are needed to understand the mechanisms of analgesic effect of this agent.

Exogenously given CDP-choline increases the choline levels in plasma and several tissues, including brain [27]. The increases in brain choline concentrations result in concomitant increase in synthesis and release of ACh [28]. Therefore, it is possible that the observed antinociceptive activity of CDP-cho-

line could be due to the activation of presynaptic cholinergic mechanisms by increasing brain choline levels. The inhibition of the effect of CDP-choline by HC-3 pretreatment (Figure 3), a neuronal high-affinity choline uptake blocker supports this hypothesis.

The activation of central cholinergic nicotinic receptors appears to mediate the effect of CDP-choline against OXA-induced neuropathy as mecamylamine pretreatment blocked the antinociceptive response to CDP-choline while atropine did not change the effect of CDP-choline. Additionally, the antagonistic effect of α-BgTx on CDP-choline-induced antinociception suggested the involvement of α7 nAchRs.

The lack of antagonistic effect of naloxone pretreatment on the antinociception produced by CDP-choline excluded a possible involvement of opioid receptors in the mediation of this effect (Figure 6). On the other hand, $GABA_B$ receptor antagonist CGP-35348 effectively attenuated the antinociceptive responses to CDP-choline (Figure 6). This finding is consistent with the results reported in the literature [12,14], and suggest that a possible interaction between GABAergic and cholinergic system by implicating supraspinal $GABA_B$ receptors in the mediation of the CDP-choline-induced antinociceptive effects in OXA-induced neuropathic pain.

In conclusion, the results of this study indicate that CDP-choline is able to produce an antihyperalgesic effect in OXA-induced neuropathic pain by mainly potentiating endogenous cholinergic activity. The activation of central nicotinic receptors, predominantly α7 nAChRs, through the activation presynaptic cholinergic mechanisms, mediates the antinociceptive responses to this agent. This study also has provided some evidence that $GABA_B$ receptors may be involved, at least in part, in the short-lived antihyperalgesic activity of CDP-choline. CDP-choline is available in both tablet and capsule form. After its absorption from the intestinal wall, CDP-choline is widely distributed throughout the body, and easily crosses the blood-brain barrier [10]. Therefore, the encouraging results in this animal experiment may prompt further clinical evaluation of CDP-choline in the management of OXA-induced neuropathic pain.

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