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Short communication

Antinociceptive effect of lidocaine in rats

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Abstract:
Lidocaine, a local anesthetic drug, exerts its effect by blocking sodium channels in peripheral sensory neurons. It is commonly used in clinical practice as a local anesthetic drug. This study was undertaken in order to determine the effect of lidocaine on sodium channels in neurons of the central nervous system and its modulatory effect on the pain perception in rats. Therefore, the effect of direct lidocaine administration *icv* on pain perception in rats exposed to noxious thermal stimuli was determined. A significant long-lasting antinociceptive effect of lidocaine injected at the doses ranging between 0.065–1.3 μmol (17.5–351 μg, respectively) was documented. It was concluded that intracerebral administration of sodium channel blockers might be a useful method in the study of pain perception in the brain.

Keywords:
pain, lidocaine, intracerebroventricular administration, rat

Abbreviations: *icv* – intraventricular (into the lateral brain ventricle), *ip* – intraperitoneal, *iv* – intravenous

Introduction

The isoforms of voltage-gated sodium channels are abundantly distributed in neurons of the peripheral nervous system, in the spinal cord and in different brain areas [2, 3] as well as in glial cells [8].

Lidocaine, a local anaesthetic drug, is a sodium channel blocker, as it blocks voltage-gated sodium-channels [10, 14, 25] and, to a much lesser degree, K^+ and Ca^+ channels [26]. Local anesthetics bind to the inner pore of sodium channels [6]. Lidocaine binding to the inner vestibule of the Na^+ channel inhibits the process of ultra-slow inactivation of this channel acting as a "foot in the door" in the inner vestibule [21]. Moreover, it has been postulated that lidocaine also binds to fast-inactivated sodium channels [13]. These mechanisms stabilize the open state of voltage-dependent sodium channels in the central nervous system [5]. Apart from the most frequent application of lidocaine for topical anesthesia, also *iv* administration of this drug exerted analgesic effect in different kinds of pain [22, 24]. A clinical case of a patient suffering from persistent central pain after encephalitis who had long-term pain relief after several repeated *iv* infusions of lidocaine was reported [4] and the role of the posterolateral thalamus in the mechanism of lidocaine effect was postulated [4]. Moreover, it was demonstrated that *iv* lidocaine had an evident inhibitory effect on spinal neurons excited by colorectal distension in rats [17]. The probable mechanism of this effect was a lidocaine-induced decrease in responsiveness of the colorectal distension-sensitive receptors in the spinal neurons [17]. But *ip* injection of lidocaine was without any effect on mechanical or cold allo-

dynia in the model of neuropathic pain in rats [7]. There are only a few reports on the effect of lidocaine on responsiveness of neurons mediating pain perception in the rat brain, and the antinociceptive effect of this drug [15].

The present study was undertaken in order to determine the effect of direct lidocaine administration *icv* on pain perception in rats exposed to noxious thermal stimuli.

The results of the present study may demonstrate a possibility of pain treatment by lidocaine administration directly *icv*, therefore, by blocking sodium channels in neurons of the brain.

Materials and Methods

The protocol of this study was approved by the ethical committee of the Medical University of Silesia (L.dz. NN-0-43-57/99).

Animals

The studies were performed on adult (280–320 g) male Wistar rats obtained from the Animal Farm of the Medical University of Silesia in Katowice. The animals were kept under 12 h light : 12 h dark cycle (light from 6 am to 6 pm) with free access to standard food and water.

Experimental protocol

A week before the experiments polyethylene cannulas (TOMEL, Tomaszów Mazowiecki, Poland) were implanted into the lateral brain ventricle using the same technique as in our previous study [19, 20]. Rats were anaesthetized with chloral hydrate (POCH, Gliwice, Poland) anesthesia (300 mg/kg, *ip*) and polyethylene cannulas (TOMEL, Tomaszów Mazowiecki, Poland) were introduced *icv* at the following coordinates: 2 mm to the right from the sagittal suture, 2 mm behind the coronary suture at a depth of 4 mm from the surface of the skull, and were fixed to the skull bones with glue Duracryl (Spofa Dental, Prague, Czech Republic), and were allowed for a recovery and adapted to handling by an experimenter.

On the day of the experiment, every dose of lidocaine hydrochloride (Jelfa, Jelenia Góra, Poland) dissolved in a constant volume of 5 µl of 0.9% NaCl was administered *icv* using a Hamilton microsyringe. Antinociceptive effect was determined by two methods: by the hot-plate test [18] and tail immersion test [11] before and at the following time intervals: 5, 15, 30, 45, 60, 90, 120 min and 24 h after the injection. The temperature of the hot-plate and the hot water in the tail immersion test was 56°C. Nociceptive reaction of animals in the hot-plate test was expressed as paw-licking and limb withdrawal [18], while in the tail immersion test, the tail withdrawal from container with hot water was recorded [11].

The determined latency time for each animal was converted to the percent of analgesia according to the formula:

$$\text{\% of analgesia (\% of maximal antinociceptive effect)} = \frac{T_x - T_o}{T_{max} - T_o} \times 100$$

where: T_x – is the individual latency time determined at appropriate intervals after lidocaine administration, T_o – individual latency time determined before lidocaine injection, T_{max} – maximal latency time was 20 s in the hot-plate test and 10 s in the tail immersion test.

At the end of the experiment, the rats were sacrificed by chloral hydrate overdosing (900 mg/kg, *ip*), and the placement of the tips of the cannulas was controlled by *icv* injection of Indian ink solution and visual inspection of the lateral brain ventricle.

Data were subjected to ANOVA and the *post-hoc* Dunnett test (significance $p < 0.05$). All these experiments were performed in accordance with guidelines for investigations of experimental pain in conscious animals [27].

Results

Lidocaine injected *icv* at doses of 0.065; 0.13; 0.65 and 1.3 µmol (17.55 µg, 35.1 µg, 175.5 µg, 351 µg, respectively) exerted at all doses uniformly evident antinociceptive effect in rats, lasting 120 min, as determined by means of the tail immersion test (Fig. 1). On the other hand, significant antinociceptive effect of lidocaine determined by the hot-plate test was observed at the same time intervals after its *icv* administration at the dose of 0.13 µmol (Fig. 2). The lower dose of lidocaine 0.65 µmol *icv* (175.5 µg) induced a significant antinociceptive effect only 30 and 45 min after injection (Fig. 2), while such significant

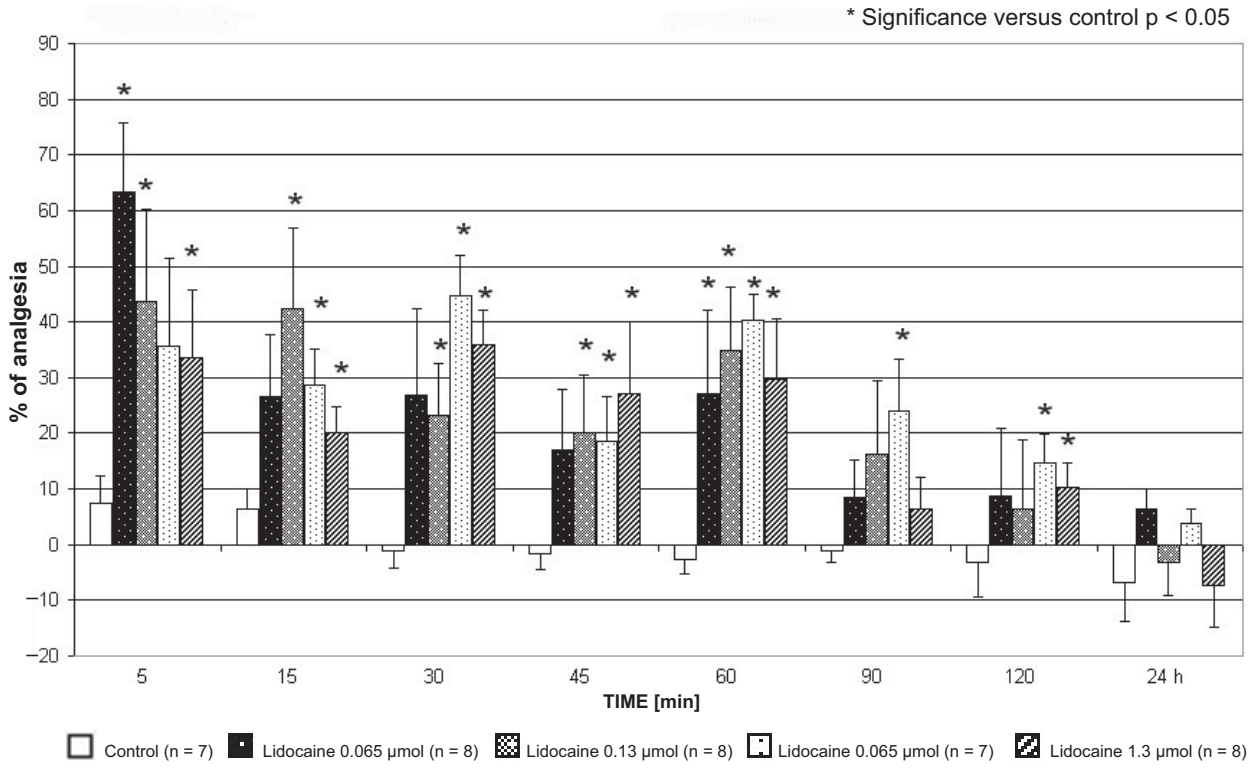

Fig. 1. Antinociceptive effect of lidocaine in the tail immersion test

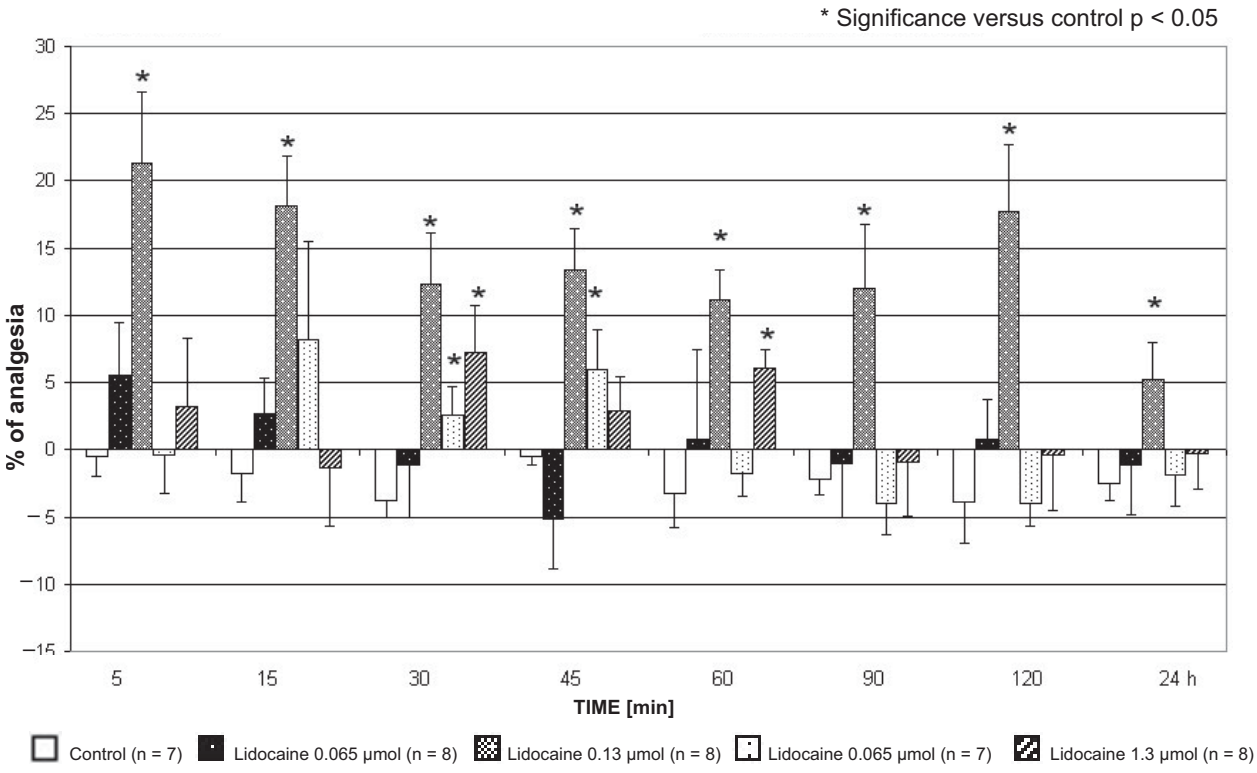

Fig. 2. Antinociceptive effect of lidocaine in the hot plate test

effect of this drug injected *icv* at the dose of 1.3 μmol (351 μg) was observed at 30 and 60 min after administration (Fig. 2).

Discussion

The results presented here indicate that *icv* administration of lidocaine induced prominent antinociceptive effect in rats. This effect appeared immediately after lidocaine administration and was long-lasting. This effect was demonstrated in both tests used, despite that it was more pronounced in the tail immersion test.

Both these tests have been used to assess rat response to a painful thermal stimulus. This effect was not dose-dependent as the lower used lidocaine dose of 0.065 μmol and the 20-fold higher dose of 1.3 μmol induced similar significant antinociceptive effect in the tail immersion test. The enhancement of the range of used lidocaine doses would indicate a dose-dependent effect. However, higher *icv* doses of lidocaine were shown to induce convulsive effect in rats which makes impossible to determine the nociceptive reaction. The dose of 1.3 μmol *icv* is a threshold convulsive dose in rats [Plech A. and Gibiec S., unpublished data]. Moreover, the lower dose of 0.065 μmol *icv* seems to be a threshold antinociceptive dose as it was ineffective in the hot plate test. Further study is necessary to define lidocaine effect. The lack of the dose-dependent lidocaine effect may be, also due to other lidocaine effects. It was found that it interacts with central dopaminergic receptors in rats. However ip injection lidocaine at the dose of 60mg/kg did not induce changes of the relase of DOPAC in rats striatum, determined in vivo using a differential pulse voltametry method [23]. The depletion of brain amines, norepinephrine and dopamine, increased susceptibility to seizure activity in rats and mice [12]. Pretreatment of rats with inhibitors of monoamine synthesis, α-methylp-tyrosine and p-chlorophenylalanine increased the threshold for lidocaine-induced convulsions [1]. Moreover, Gibiec and Plech demonstrated that central D_1 dopamine receptors were involved in the neurotoxic convulsive effect of lidocaine, as lidocaine-induced convulsions were completely prevented by a D_1 antagonist SCH 23390 [9]. But at present, there are no data on the role of central monoamines in the mechanism of lidocaine-induced analgesia. Lidocaine injected *icv* principally modulates activity of brain neurons expressed as a prominent, long-lasting antinociceptive effect because it penetrated from the lateral brain ventricle into adjacent parts of the brain, therefore, also into the posterolateral thalamus. This nucleus is a common target of ascending pain pathways. Cahana et al. [4] demonstrated by positron emission tomography a relative hypoactivity of the left posterolateral thalamus of a patient with chronic neuropathic pain. *Iv* administration of lidocaine caused pain relief with concomitant disappearance of thalamic hypoactivity [4]. Thus, the result of the present study indicates the central mechanism of lidocaine-induced analgesic effect. As a primary mechanism of action of lidocaine, like of other anesthetics, is the blockade of sodium channels [10, 14, 16, 25], one can infer that the lidocaine-induced blockade of sodium channels spreads in neurons of different brain areas distinctly depressing their excitability increased by peripheral noxious thermal stimuli, which is manifested as antinociceptive effect.

Conclusion

The obtained results indicate that intracerebral administration of sodium channel blockers may be a useful method in the study of the mechanism of pain perception in the brain.

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