Xenon Blocks the Induction of Synaptic Long-Term Potentiation in Pain Pathways in the Rat Spinal Cord *In Vivo*

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BACKGROUND: Xenon's (Xe) mechanisms for producing anesthesia and analgesia are not fully understood. We tested the effect of Xe equilibrated in a lipid formulation or normal saline on spinal C-fiber-evoked potentials and on the induction of synaptic long-term potentiation (LTP).

METHODS: C-fiber-evoked field potentials were recorded in the superficial lumbar spinal cord in response to supramaximal electrical stimulation of the sciatic nerve. Anesthesia was maintained with isoflurane in one-third O_2 and two-thirds N_2O. Xe equilibrated at a concentration of 600 μL/mL of Lipofundin MCT® 20%, (n = 5) or solvent alone (n = 3), and Xe equilibrated at a concentration of 100 μL/mL of normal saline (n = 7) or saline alone (n = 7) was given IV under apnea. High-frequency stimulation of the sciatic nerve was applied 60 min after the injection of Xe-containing formulations or solvents [to induce LTP].

RESULTS: High-frequency stimulation potentiated C-fiber-evoked potentials to 156% ± 14% (mean ± SEM) of control. Low-dose Xe in saline 0.9% blocked the induction of LTP. High-dose Xe equilibrated in MC® 20% showed no additional effect when compared with the solvent, which blocked the induction of LTP.

CONCLUSION: Low-dose Xe in saline 0.9% revealed no antinociceptive, but preventive, action in spinal pain pathways.

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Xenon (Xe) is a noble gas with interesting anesthetic and analgesic properties. It has been investigated as an inhaled anesthetic because it provides effective and safe anesthesia with the advantages of hemodynamic stability and rapid recovery (1). Xe's underlying molecular mechanisms for the production of anesthesia and analgesia are not fully understood (2,3). Studies have produced inconclusive results, depending on the species used and whether *in vivo* or *in vitro* techniques were applied (4–8). Xe is thought to induce anesthetic action by potent noncompetitive inhibition at glutamatergic receptors of the *N*-methyl-D-aspartate (NMDA) subtype *in vitro* (3). This result could, however, not be reproduced in nematodes *in vivo* (8). Xe in aqueous solutions reduces glutamate-, α-amino-3-hydroxy-5-methyl-4-isoxazolole propionate (AMPA)-, and kainate-induced membrane currents *in vitro* (9).

Xe is extremely rare, and therefore expensive. An alternative to inhaled administration of volatile anesthetics is the IV use of inhaled anesthetics dissolved in lipid emulsions (10). The main advantages of this formulation are cost reduction due to the need for minimal anesthetic equipment and decreased MAC (11). This form of administration would be especially useful in the case of the expensive volatile anesthetic Xe. Equilibration of Xe in lipid emulsions results in high Xe concentrations (12). However, lipid emulsions on their own reveal action on NMDA receptors (NMDAR) (13,14).

We tested, for the first time, Xe equilibrated in both aqueous solution and lipid emulsion for IV administration. We found that low doses of Xe in aqueous solution results in long-lasting prevention of synaptic long-term potentiation (LTP) in the spinal dorsal horn *in vivo* which is a mechanism of pain amplification (15).

METHODS

Animals

After governmental approval, experiments were performed on male Sprague-Dawley rats weighing 250–290 g (Charles River Deutschland, Sulzfeld, Germany). Animals were kept under temperature-controlled environmental conditions on a 12–12 h light–dark cycle and were fed standard diet (Altromin

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C 1000; Altromin, Lage, Germany) with access to food and water *ad libitum*.

Preparation of the Animals

Preparation of the animals is described in detail elsewhere (16). Briefly, isoflurane in two-thirds N_2O and one-third O_2 was used to induce (3.5 vol % inspiratory) and maintain (1.0 vol % expiratory) anesthesia. The femoral vein and artery were cannulated, the trachea was intubated to allow mechanical ventilation. The left sciatic nerve was dissected free for bipolar electrical stimulation and lumbar segments L4 and L5 of the spinal cord were exposed by laminectomy.

Electrophysiological Recordings and Nerve Stimulation

In response to electrical stimulation of the sciatic nerve, field sum potentials were recorded with glass microelectrodes (3–5 MΩ) 300–600 μm from the dorsal surface of the spinal cord dorsal horn (laminae I and II). Recordings were made with an ISO-DAM-amplifier (World Precision Instruments, Sarasota, FL). C-fiber-evoked field potentials that were characterized by a negative focus in superficial spinal dorsal horn, long latencies (90–120 ms, corresponding to conduction velocities <1.2 m/s), and by high thresholds (10–25 V) were investigated further (insets, Fig. 2). Intensity for the test stimulus (10–25 V, 0.5 ms, 5 min intervals) was adjusted for each animal to achieve a stable C-fiber-evoked potential. For induction of LTP, a high frequency stimulus (HFS) consisting of four trains of 100 Hz, 40–50 V, 0.5 ms pulses for 1 s at 10 s intervals was applied. Conditioning stimulation was always higher than test stimuli and 40 V were used if test stimuli were lower than 20 V. Conditioning stimulation consisted of 50 V when the intensity of test stimuli was over 20 V.

Preparation of Xe-Containing Solutions

To produce Xe-containing solutions, we equilibrated Xe in either commercially available saline 0.9% or in commercially available Lipofundin MCT® 20% purchased from Braun-Melsungen (Melsungen, Germany) (9,12). A Xe concentration of both saturated solutions was measured from the formulations ready for injection by static headspace gas chromatography mass spectrometry (headspace GCMS) as described earlier (12). Xe was obtained from Messer GmbH (Krefeld, Germany).

Experimental Procedures

Animals were randomly included in the following experimental protocol illustrated in Figure 1. With the animal model we used, we could investigate the influence of IV-administered substances on C-fiber-evoked potentials (pre-HFS), on the induction and the maintenance of LTP (post-HFS) in the rat spinal cord *in vivo*.

1. To establish LTP under deep isoflurane anesthesia (n = 7), test stimuli were given to achieve baseline recordings for 60 min (baseline, Figure 1). Two boli of 0.5 mL normal saline were administered in the identical infusion regime as Xe-containing solutions (see later). Test stimuli and recording were continued for another 55-min period (pre-HFS, Fig. 1). Then conditioning HFS was applied to the sciatic nerve and responses to test stimuli were recorded for 60 min (post-HFS, Fig. 1).
2. To test the effect of high-dose Xe (12.4 mg/kg body weight; n = 5) on C-fiber-evoked potentials and on the induction of LTP, Lipofundin MCT® 20% fully saturated with Xe (12) was given after 60 min of baseline recording. The infusion regime mentioned later was used to avoid excess pulmonary loss of Xe by exhalation and to prevent unspecific effects of IV injection of a single 1 mL bolus. The infusion regime was guided by the observation that breath-holds of 20 s decrease oxygen saturation in rats by 0.05% only (17).
   - After 50 min baseline recording, animals were ventilated with 100% O_2 for 10 min and blood gas analysis was performed (baseline, Figure 1).
   - The anesthetic machine was stopped and 0.5 mL Xe-containing Lipofundin MCT® 20% was injected IV over a period of 5 s. The catheter was flushed with 0.1 mL saline 0.9%. Then the anesthetic machine was switched on again and blood gas analysis was performed. The time of apnea was 30 s.
   - The animal was ventilated with 100% O_2 for 1 min, then the anesthetic machine was stopped again and 0.5 mL Xe-containing Lipofundin MCT® 20% was injected IV over a period of 5 s. The catheter was flushed with 0.1 mL saline 0.9% and time of apnea was

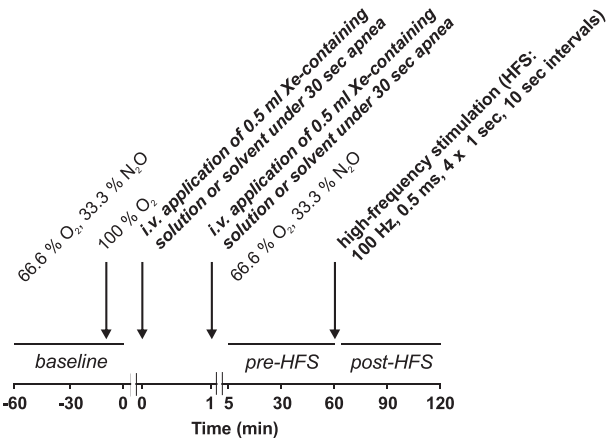

Figure 1. Experimental protocol of the infusion regime used to avoid excessive loss of Xenon (Xe) by exhalation and to prevent unspecific effects of injection of a single 1 mL bolus. Baseline was achieved by test stimuli and recordings in 5 min intervals (baseline). IV administration of Xe-containing solutions or saline was performed twice under apnea of 30 s each. The effect of applied substances on C-fiber-evoked potentials was measured for 55 min (pre-HFS). Then conditioning high-frequency stimulation (HFS) was applied to the sciatic nerve and responses to test stimuli were recorded for an additional 60 min (post-HFS) to investigate the effect on induction and maintenance of long-term potentiation.

30 s. The anesthetic machine was switched on again, blood gas analysis was performed and the animal was once again ventilated with two-thirds N_2O and one-third O_2 (Fig. 1).

- Test stimuli were continued for a period of 55 min (pre-HFS). Then conditioning HFS was applied to the sciatic nerve and responses to test stimuli were recorded for additional 60 min (post-HFS, Fig. 1).

3. Lipofundin MCT® 20% alone ($n = 3$) as the solvent for Xe-containing Lipofundin MCT® 20% was given after 60 min of baseline recordings. Lipofundin MCT® 20% was injected in the same manner as Xe-containing Lipofundin MCT® 20% (as mentioned earlier). After this infusion regime, test stimuli were given for another 55 min and HFS was applied to the sciatic nerve. Responses to test stimuli were recorded for another 60 min.
4. Xe equilibrated at a concentration of 100 μL/mL of normal saline reduces glutamate-, AMPA-, and kainate-induced membrane currents in cortical neurons *in vitro* (9). Therefore we tested this low-dose Xe (2 mg/kg body weight; $n = 7$) on C-fiber-evoked potentials and on the induction of LTP. Normal saline loaded with Xe was given after 60 min of baseline recording in the above-mentioned infusion regime. HFS was applied to the sciatic nerve 55 min after the application of Xe-containing normal saline had been performed and responses to test stimuli were recorded for another 60 min.

Data Analysis and Statistics

The area under the curve of the C-fiber-evoked field potentials was determined off-line by parameter extraction which was implemented by the software Experimenter's Workbench (DataWave, CO). The area of the C-fiber-evoked field potentials was determined as the integral of the wave form. Measurements were standardized for each rat such that the mean of the respective baseline values was equal to 100. Outcome values were obtained before infusion (baseline), after infusion, but before HFS (pre-HFS) and after HFS (post-HFS). Within phases, values did not exhibit any trend in time and were averaged. Statistical analysis of these averages was based on one-way analysis of variance (ANOVA). A *post hoc* Tukey test was performed for all pair wise multiple comparison procedures. All data were tested for normality and equal variance. A significant difference was considered when $P < 0.05$. All values are expressed as mean ± SEM.

RESULTS

Amount of Xe in Saline 0.9% and Lipofundin MCT® 20%

Saturated normal saline solutions contained 97 ± 3 μL Xe · mL^{-1} and the saturated Lipofundin MCT® 20% contained 597 ± 11 μL Xe · mL^{-1}. With regard to the experimental conditions (20°C and 110 m above sea level), 1 mL Xe-saturated saline 0.9% contained 0.52 mg Xe and 1 mL Xe-saturated Lipofundin MCT® 20% contained 3.22 mg.

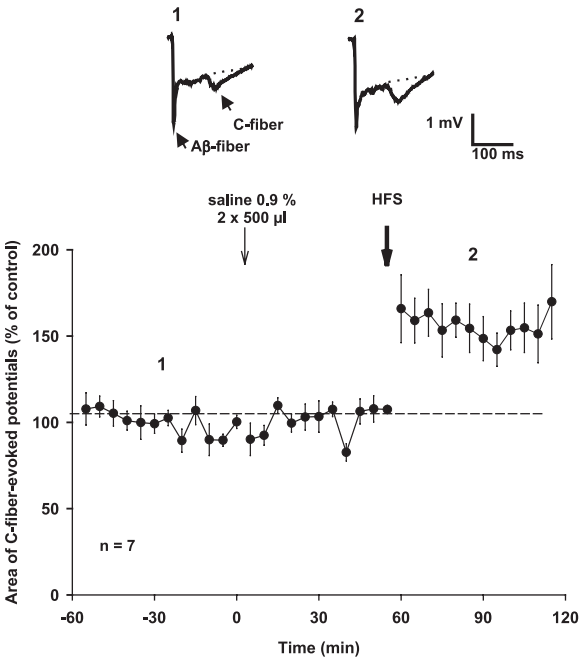

Figure 2. Long-term potentiation (LTP) of synaptic strength is induced in the superficial spinal dorsal horn by high-frequency stimulation (HFS). In each experiment, C-fiber-evoked potentials were provoked by electrical stimulation of the sciatic nerve. Mean responses ± SEM are expressed as a percentage of controls and are plotted versus time. HFS resulted in synaptic LTP during isoflurane in one-third O_2 and two-thirds N_2O ($n = 7$). Injection of two boli normal saline 0.5 mL each neither affected C-fiber-evoked potentials nor the induction of LTP by HFS. Insets show original recordings of field sum potentials during baseline and 30 min after HFS. Dotted lines demonstrate how C-fiber-evoked potentials were quantified as the integral of the wave form.

Two Breath-Holds for 30 s each after 10 min Pure Oxygen Ventilation did not Affect Pao_2

To avoid excessive pulmonary loss of Xe by exhalation, ventilation was stopped twice while 0.5 mL Xe-containing fluids were administered IV. Pao_2 increased to 317 ± 10 mm Hg ($n = 16$) during 10 min ventilation before apnea with 100% oxygen, and did not decrease after two apnea times of 30 s each. Pao_2 decreased to physiological levels after the return to ventilation with one-third O_2 and two-thirds N_2O (data not shown). Arterial blood pressure and heart rate remained stable during breath-holds and two infusions of 0.5 mL of any solution.

LTP of C-Fiber-Evoked Field Potentials was Induced Under Deep Isoflurane O_2/N_2O Anesthesia

A- and C-fiber-evoked field potentials could clearly be distinguished after stimulation of the sciatic nerve (insets, Fig. 2). The injection of normal saline had no effect on the magnitude of C-fiber-evoked potentials

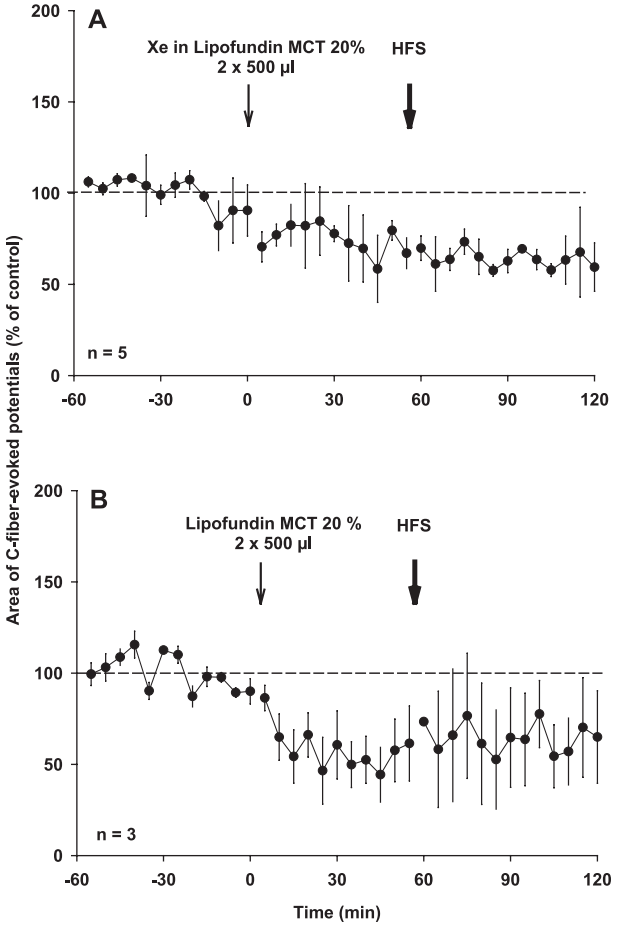

Figure 3. Xenon (Xe)-containing Lipofundin MCT® 20% blocked the induction of long-term potentiation (LTP). A. High-frequency stimulation (HFS) 60 min after application of Xe-containing lipid formulation did not induce LTP. B. Lipofundin MCT® 20% alone revealed the same effect (B; $n = 3$).

($P = 1$; Fig. 2). HFS applied to the sciatic nerve at C-fiber strength consistently induced a statistically significant LTP ($P < 0.001$) at 156% ± 14% of control in rats anesthetized with isoflurane in one-third O_2 and two-thirds N_2O ($n = 7$; Fig. 2).

Xe Equilibrated in Lipofundin MCT® 20% Showed no Additional Effects Compared to the Solvent Alone

Xe was applied IV equilibrated in Lipofundin MCT® 20% with an amount of 597 ± 11 $\mu L\ Xe \cdot mL^{-1}$ ($n = 5$). C-fiber-evoked potentials were stabile at 76% ± 13% of control (Fig. 3A). HFS administered 60 min after bolus injection of Xe-containing Lipofundin MCT® 20% did not induce LTP. C-fiber-evoked potentials remained at 63% ± 9% of control (Fig. 3A). Changes in C-fiber-evoked potentials were not statistically significant among the three time periods (baseline, pre-HFS, post-HFS) tested ($P = 0.14$).

Lipofundin MCT® 20% itself was administered IV as a control for Xe-containing Lipofundin MCT® 20% ($n = 3$; Fig. 3B). C-fiber-evoked potentials remained at 57% ± 14% of control. After HFS, C-fiber-evoked potentials were 64% ± 27% of control (Fig. 3B).

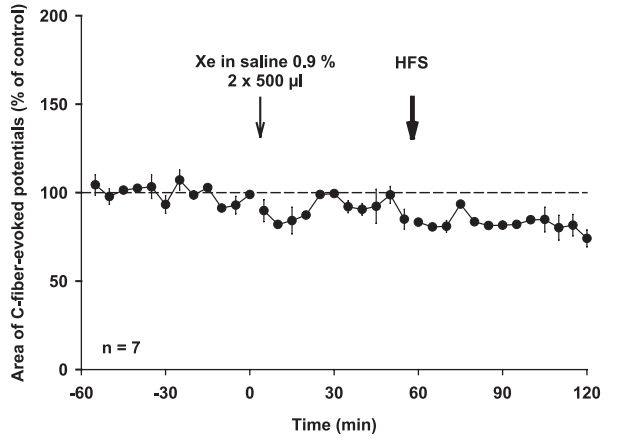

Figure 4. Xenon (Xe)-containing normal saline did not affect C-fiber-evoked potentials when administered IV 60 min after stable baseline recordings ($n = 7$). High-frequency stimulation (HFS) of the sciatic nerve was given 60 min after injection of Xe in normal saline. The induction of LTP by HFS was blocked by previously injected Xe-containing normal saline.

Changes in C-fiber-evoked potentials were not statistically significant among the three time periods (baseline, pre-HFS, post-HFS) tested ($P = 0.092$).

Low-Dose Xe in Saline 0.9% did not Affect C-Fiber-Evoked Potentials, but Blocked the Induction of LTP

Xe equilibrated in normal saline with an amount of about 100 $\mu L \cdot mL^{-1}$ was administered IV ($n = 7$). C-fiber-evoked potentials remained near baseline values of 92% ± 4% of control ($P = 0.24$; Fig. 4). HFS administered 60 min after infusion of Xe-containing normal saline did not induce LTP ($P = 0.25$). C-fiber-evoked potentials remained at values of 85% ± 3% of control (Fig. 4).

DISCUSSION

The main findings of the study are that IV Xe, administered at a low dose, blocked the induction of synaptic LTP in the rat spinal cord 60 min after application *in vivo* and thus reveals preventive action. A high dose of Xe dissolved in Lipofundin MCT® 20% had no additional effect when compared with the solvent alone.

Xe in Aqueous Solution did not Affect C-Fiber-Evoked Potentials, but Blocked LTP

The mechanisms which underlie Xe's mechanisms for the production of anesthesia and analgesia are not fully understood (2,3). Xe is thought to induce anesthetic action by potent noncompetitive inhibition at the NMDAR *in vitro* (3) which, however, could not be reproduced in nematodes *in vivo* (8). In the *in vivo* setup, we used a low concentration of Xe which did not affect C-fiber-evoked potentials in the rat spinal cord *in vivo*, i.e., Xe revealed no antinociceptive effect at or near the first synapse of pain pathways. This results in agreement with our previous studies showing that neither low doses nor even high doses of

NMDAR antagonists up to 50 mg/kg S(+)-ketamine reduce C-fiber-evoked potentials (18). The monosynaptic nociceptive transmission of field sum potentials is insensitive to NMDAR antagonists (18,19). In putative polysynaptic pathways, which are more sensitive to NMDAR blockage, inhaled Xe directly inhibits responsiveness of wide dynamic range neurons to touch and pinch in single cell recordings *in vivo* (4,5). However, we might have used IV administered Xe in a concentration too low to elicit an antinociceptive effect.

Although Xe did not affect C-fiber-evoked field potentials *in vivo*, an IV administered low dose of Xe blocked the induction of LTP of synaptic strength in nociceptive pathways. Synaptic LTP in pain pathways is a cellular model of inflammatory and postoperative pain amplification (15). Activation of NMDAR or neurokinin (NK)-receptors are necessary and sufficient for the induction of synaptic LTP in the rat spinal cord *in vivo* (19,20). Consequently, LTP is prevented by NMDAR antagonists, used both experimentally (19) and clinically (18). Previous studies corroborate our results: Xe suppresses the second phase of the formalin test (7) which is caused by altered processing of nociceptive information in the spinal cord. Furthermore, Xe suppresses c-fos expression (7,21) and the number of phosphorylated NMDAR-positive cells after formalin injection (7). Therefore, the blockade of LTP due to a low dose of Xe is thought to result from the inhibition of NMDAR. Synaptic LTP in the rat spinal cord can be achieved by the activation of NMDAR or NK-receptors. There are no data on the action of Xe on NK-receptors. However, Xe revealed action not only on NMDAR but also on non-NMDAR such as AMPA- and kainate-receptors (8,9,22). It is a possibility that Xe may reduce NK-receptors, and thereby also block synaptic LTP in pain pathways.

In our study, Xe blocked the induction of LTP in a small dose and had a long-lasting protective effect, because Xe was administered IV 60 min before the conditioning stimulus. This observation is in agreement with the results of our previous studies in which we have shown that synaptic LTP in the rat spinal cord is persistently prevented by low doses of experimentally (19) and clinically (18) used NMDAR antagonists. Activation of the NMDAR is the pivotal point in the induction of synaptic LTP (15). Consequently, only low doses of NMDAR antagonists are sufficient to prevent LTP in the rat spinal cord that otherwise lasts for more than 8 h after induction (19).

Xe uptake is extremely fast when given as an inhalant because of its lipophilic nature, which results in a very low blood/gas partition coefficient of 0.17 (23). Magnetic resonance imaging using ^{129}Xe showed an arterial transit time of 4 s for the brain and rapid accumulation in the white matter and the myelin (23). Once accumulated in the brain, the lipophilic Xe remains there, which is reflected by an extremely high tissue/blood partition coefficient of 17 (23). However, there are no data on decay time for ^{129}Xe from white matter or myelin in the literature.

Nitrous oxide (N_2O) has potency as an NMDAR antagonist *in vitro* (6,24), in single cell recordings (4,5) and in behavioral experiments *in vivo* (7,21). In the experimental set up we used, however, C-fiber-evoked potentials were not affected by two-thirds N_2O and one-third O_2 when compared with 100% O_2 (unpublished data). This can be explained by the fact that monosynaptic nociceptive transmission is relatively insensitive to NMDAR antagonists (18,19) as discussed earlier.

Lipofundin MCT® 20% Blocks LTP

IV administration of inhaled anesthetics dissolved in lipid emulsions have rarely been investigated (10,11). The main advantages of this formulation are cost reduction due to a minimal requirement for anesthetic equipment (i.e., only an infusion pump is needed) and decreased MAC (11), together with rapid induction and emergence from anesthesia. In pure lipid solutions, approximately sixfold amounts of Xe can be dissolved compared to aqueous solutions (12). Lipid emulsions might therefore serve as an appropriate carrier for the lipophilic Xe from which it is released to different compartments according to its partition coefficient, being highest for white matter and myelin (23).

The commercially available Lipofundin MCT® 20% is an oil-in-water formulation that reduces NMDA-evoked currents in a dose-dependent manner in cultured cortical neurons (14). The exact mechanism for this reduction is unknown. Two possible causes are discussed (14): suppression of phosphorylation of the NMDAR could lead to a reduction of NMDA-evoked currents. Second, trapping of the agonist NMDA or the co-agonist glycine in the lipid solution might be the cause for reduced NMDA-evoked currents (14). Further *in vitro* studies would reveal the mechanisms. As mentioned earlier, the blockade of NMDAR does not reduce C-fiber-evoked field potentials *in vivo* under the same experimental conditions we used (18,19). Thus, additional effects of Xe, e.g., on non-NMDAR such as AMPA- and kainate-receptors (8,9,22), may be involved in the action of Xe on C-fiber-evoked potentials *in vivo*.

Although, in our experimental model, even high doses of NMDAR-blocking substances did not affect C-fiber-evoked potentials, as discussed earlier, blockade of NMDAR or NK-receptors is necessary and sufficient to prevent the induction of synaptic LTP in the rat spinal cord (18,19). Lipofundin MCT® 20% reduces NMDA-evoked currents *in vitro* (14). Therefore we assume that, in this study, Lipofundin MCT® 20% blocked the induction of LTP due to blockade of NMDAR.

In conclusion, a dose of Xe equilibrated in saline prevents sensitization in pain pathways in the rat spinal cord *in vivo*, most likely via NMDAR blockage.

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