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Xenon-induced changes in CNS sensitization to pain

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ABSTRACT

Electrophysiological investigations of the spinal cord in animals have shown that pain sensitizes the central nervous system via glutamate receptor dependent long-term potentiation (LTP) related to an enhancement of pain perception. To expand these findings, we used functional magnetic resonance (fMRI), blood oxygen level dependent (BOLD) and perfusion imaging in combination with repeated electrical stimulation in humans. Specifically we monitored modulation of somatosensory processing during inhibition of excitatory transmission by ocular application of the glutamate receptor antagonist xenon. BOLD responses upon secondary stimulation increased in mid insular and in primary/secondary sensory cortices under placebo and decreased under xenon treatments. Xenon-induced decreases in regional perfusion were confined to stimulation responsive brain regions and correlated with time courses of xenon concentrations in the cranial blood. Moreover, effects of xenon on behavioral, fMRI and perfusion data scaled with stimulus intensity. The dependence of pain sensitization on sufficient pre-activation reflects a multistage process which is characteristic for glutamate receptor related processes of LTP. This study demonstrates how LTP related processes known from the cellular level can be investigated at the brain systems level.

Introduction

Pain-induced sensitization describes an enhanced responsiveness of nociceptive neurons to their normal afferent input (Sandkühler, 2007). For example, after sunburn a normally warm shower feels extremely hot (Ji et al., 2003). This phenomenon has been extensively investigated in spinal cord neurons of experimental animals using electrophysiological methods. An enhanced responsiveness following use-dependent strengthening of synaptic transmission has been demonstrated which leads to a reduction in pain threshold and an amplification of pain responses. Analysis of the underlying mechanisms have shown that generation and maintenance of pain-induced sensitization have striking similarities with long-term potentiation (LTP) (Woolf and Salter, 2000; Sandkühler, 2007) which is known from memory research (Ji et al., 2003; Kim and Linden, 2007; Cooke and Bliss, 2006). LTP has originally been described as a long-lasting enhancement of postsynaptic field potentials in the hippocampus due to a brief high-frequency conditioning stimulus (Bliss and Lomo, 1973) and was interpreted as an increase in the efficacy of synaptic transmission (Bliss and Collingridge, 1993; Malenka and Bear, 2004).

Opening of ionotropic glutamate receptors of the *N*-methyl-D-aspartate type (NMDAR; Ikeda et al., 2003, 2006; Liu and Sandkühler, 1995) is known to be required for induction of LTP, and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic receptors (AMPAR) are thought to be important for the expression of synaptic changes (Zhuo, 2009). AMPAR mediate fast excitatory transmission involving both innocuous and acute nociceptive input, whereas in normal activity the NMDAR are inactive. However, with repeated and more intense stimuli, sufficient amounts of glutamate and peptides are released, resulting in removal of the magnesium block from the NMDAR channel. Calcium ions flow through the receptor channel, causing massive neuronal depolarization and an increased excitability of the neurons. This effect manifests itself in a decrease in pain threshold and an enhanced response to stimulation (Woolf and Salter, 2000; Ji et al., 2003). Thus, activation of NMDAR in the central nervous system triggered by sufficient afferent input from the periphery results in LTP-related sensitization (Klein et al., 2004, 2006; Sandkühler, 2007). Animal and human studies have shown that NMDAR antagonists like ketamine and dextromethorphan can reduce hyperexcitability (Liu and Sandkühler, 1995; Park et al., 1995; Ilkjaer et al., 1996; Benrath et al., 2005; Kissin, 2005).

The noble gas xenon derives its name from the Greek “stranger” because of its rarity, representing no more than 8.75×10^{-6} % of the

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atmosphere. For more than 50 years (Cullen and Gross, 1951) xenon has been used in clinical anesthetic practice and has proven to be a potent anesthetic with analgesic and neuroprotective properties (Lachmann et al., 1990). Current evidence strongly indicates that xenon inhibits excitatory glutamatergic signaling. NMDAR antagonism is regarded as the prime mechanism by which xenon exerts its effect *in vivo*, although there is an ongoing controversy whether non-NMDA receptors like AMPAR additionally contribute to the effect of the noble gas (Franks et al., 1998; Plested et al. 2004; Preckel et al., 2006; Benrath et al., 2007; Laitio et al., 2007; Salmi et al., 2008; Derwall et al. 2009).

While electrophysiological prediction of enhanced responsiveness at the neuronal level in the spinal cord provides direct access to neuronal signal changes, functional magnetic resonance imaging (fMRI) provides a complementary and non-invasive measure of signal changes at the systems level. Blood-oxygen-level-dependent (BOLD) fMRI signals are now widely accepted as a surrogate marker of local field potentials. These potentials reflect incoming sensory information that directly affects postsynaptic neurons via glutamate receptors (Logothetis et al., 2001; 2008; Mukamel et al., 2005; Niessing et al., 2005). Therefore, enhanced responsiveness to repeated sensory stimulation should be represented by increased BOLD responses. However, inference of effects from BOLD increases between successive stimulation would still depend on the choice of statistical thresholds and may additionally reflect unspecific signal gain.

Here, we make use of the inhibition of ionotropic glutamate receptors mediated by xenon with the general hypothesis that regions of sensitization in the brain should show both an increase of activity during the second stimulation under air and decreased activation under xenon due to the regional glutamate receptor antagonism. More generally, the rationale of the study was to use a defined pharmacological mechanism in combination with BOLD fMRI signals as a non-invasive surrogate marker of local postsynaptic field potentials in order to delineate rather to statistically infer brain regions of sensitization.

Additionally, the inflow of xenon or air following the first conditioning stimulation experiment (BOLD 1) was monitored by means of continuous arterial spin labeling (CASL; e.g., Wang et al., 2005). CASL provides a measure of the neural metabolism in terms of regional cerebral blood flow (rCBF) which most likely reflects the energetically demanding synaptic activity in a specific brain region (Logothetis et al., 2001; Wang et al., 2005). Changes of perfusion can therefore be regarded as a surrogate marker of altered neuronal activity.

Behaviorally, we expected a modulating effect of xenon on rating decisions of stimulus intensities. This effect was concluded from treatment-by-time interactions predicting that alterations should be more pronounced under xenon than under air.

Functionally, modulation of sensory processing should also be evident in terms of significant treatment (*air*, *xenon*)-by-time (*pre*, *post*) interactions predicting that reductions of BOLD signals in the second stimulation experiment (Fig. 1, BOLD 2) should emerge under xenon but not under air. This interaction analysis was the main test of our general hypothesis together with the additional prediction that significant interactions should be evident mainly for higher stimulation intensities. Higher and more painful intensities should be sufficient to lead to NMDAR-related massive neuronal depolarization as a condition precedent for xenon to exert its antagonistic effects.

Due to reduced synaptic activity following glutamatergic excitatory transmission, arrival of xenon at the brain metabolism should result in local decreases of rCBF in fMRI perfusion measurements (Laitio et al., 2007; Salmi et al., 2008). These decreases in neural

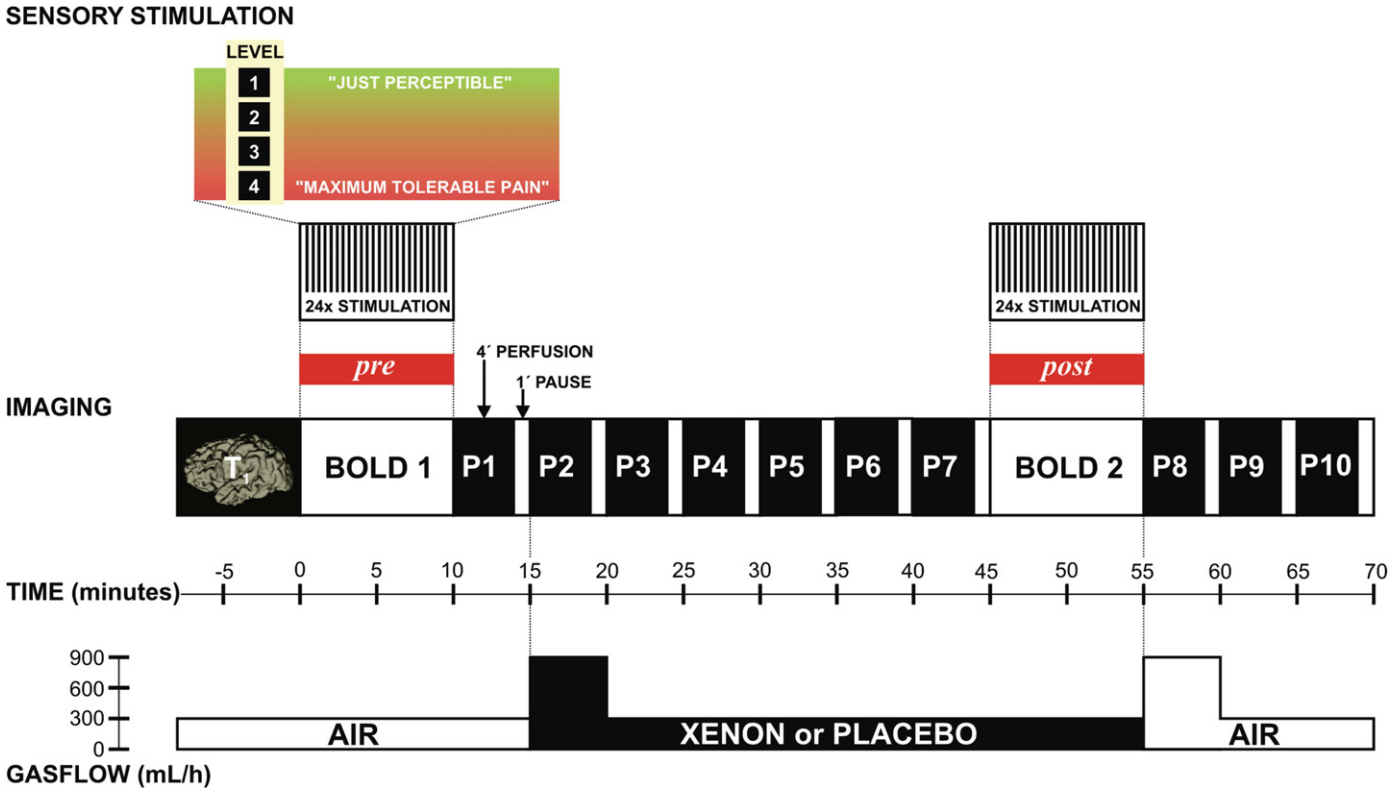

Fig. 1. Time course of an experimental session. Subjects were acquainted with MR imaging during image acquisition of their brain anatomy (T1 weighted 3D MPRAGE). Subsequently, the first stimulation experiment was performed (*pre*, BOLD 1). Next, the first of 10 resting-state perfusion blocks was acquired (P1). As for all imaging sessions P1 was always under air in order to serve as a perfusion baseline measurement. Depending on the treatment assignment protocol the subsequent six perfusion blocks (P2–P7) were measured either under air or xenon. Each block lasted 4 min and was separated from the next block by an interval of 1 min. The treatment continued during the second stimulation experiment (*post*, BOLD 2) which used identical stimulus intensities as in BOLD 1 but was ordered according to a different pseudo-random sequence. Each BOLD experiment lasted about 10 min. At the end of BOLD 2 xenon was either replaced by air, or application of air continued for another 15 min during three final perfusion blocks (P8–P10).