Effect of intravenous lidocaine on brain activation during non-noxious and acute noxious stimulation of the forepaw: A functional MRI study in the rat

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BACKGROUND: Lidocaine when administered systemically at doses that result in low plasma concentrations in the range of 2-10μg/ml can alleviate acute pain and chronic neuropathic pain in humans and experimental animal models. Interestingly, when effective, pain relief after a single intravenous (i.v.) lidocaine treatment can last for days or months, which is far beyond lidocaine's known pharmacokinetic longevity. The mechanism(s) underlying lidocaine's analgesic effect when administered systemically is poorly understood but clearly not related to interruption of peripheral nerve conduction. Other targets for lidocaine's analgesic action(s) have been suggested including sodium channels and other receptor sites in the central nervous system (rather than in the periphery). To our knowledge the effect of lidocaine on the brain's functional response to pain has never been investigated. We therefore characterized the effect of systemic lidocaine on the brain's response to innocuous and acute noxious stimulation in the rat using functional magnetic resonance imaging (fMRI).

METHODS: Alpha-chloralose anesthetized rats underwent functional magnetic resonance imaging (fMRI) using blood-oxygen-level-dependent (BOLD) contrast to quantify brain activation patterns in response to innocuous and noxious forepaw stimulation before and after IV administration of lidocaine. All imaging was performed on a superconducting 9.4T/210 horizontal bore magnet (Magnex) controlled by an ADVANCE console (Bruker). We used a single shot echo-planar sequence with the following parameters: TR=1500; TE=30ms;effective bandwidth=227272Hz, field of view=2.56 x 2.56 cm^2; 64x64 matrix with a resulting in-plane resolution of 400 μm; eight axial 1.4mm-thick slices spaced 0.15 mm apart. The innocuous forepaw stimulation with 2mA paradigm consisted of 23 scans acquired during rest, 10 scans acquired during stimulation followed by a post-stimulation rest period of 30 scans. To minimize painful exposures to the higher stimulation currents the noxious 8mA paradigm consisted of 13 pre-stimulation scans, 1 scan during stimulation (3s) and 22 scans acquired after stimulation. Lidocaine was administered intravenously (i.v.) in escalating doses of 1, 4 and 10mg/kg. Following each of the i.v. lidocaine challenges forepaw stimulation trials were conducted at 5-min, 15-min, 25-min and 35-min. One hour was allowed between each dose of lidocaine to assure that the lidocaine plasma concentration was negligible (<0.2μg/ml) before the next dose was administered.

RESULTS: Innocuous forepaw stimulation with 2mA elicited brain activation only in the contra-lateral primary somatosensory (S1) cortex. However, acute noxious forepaw stimulation with 8mA induced activation in brain areas associated with pain perception including the secondary somatosensory cortex (S2), thalamus, insula and limbic regions (Fig. 1). Under control conditions the BOLD signal amplitude and total activated pixel volume in S1/S2 elicited by forepaw stimulation with 8mA for 3s was 5.8±0.4% and 7.4±2.6 mm^3, respectively.

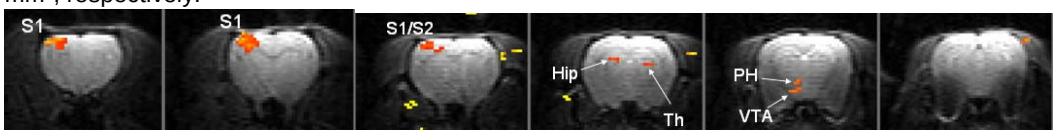

Figure 1: Brain activation map during forepaw stimulation with 8mA for 3s. Brain regions with statistically significant BOLD signal increases was observed contra-lateral to the forepaw stimulated in the following regions: primary somatosensory cortex (S1), secondary somatosensory cortex (S2), hippocampus (Hip), posterior hypothalamus (PH) and ventral tegmental area (VTA). Thalamic (Th) activity was also observed ipsilateral to the forepaw stimulated.

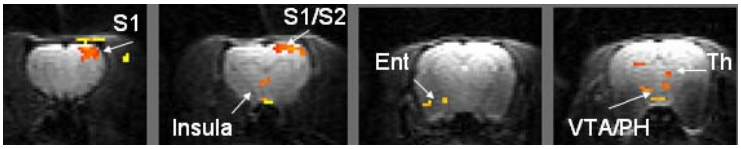

Figure 2: Brain activation patterns in response to the nociceptive 8mA stimulus (left forepaw) 5-min following 10mg/kg lidocaine. As can be seen brain activation is elicited contra-lateral in the right in S1, VTA, thalamus and posterior hypothalamus regardless of the lidocaine exposure.

Quantitative analysis showed that the amplitude of the BOLD signal immediately after the intravenous 10mg/kg lidocaine challenge was 6.9% and significantly higher than at baseline. In addition, analysis of the 4mg/kg and 10mg/kg lidocaine brain activation maps, demonstrated that the total volume of activated S1/S2 cortex was significantly larger than that observed during control conditions. For example, 5-min after the 4mg/kg lidocaine challenge the activated pixel S1/S2 volume increased from 7.4 mm^3 to 15.7mm^3 and for the 10m/kg lidocaine challenge it increased from 7.4mm^3 to 19.2mm^3

CONCLUSION: The major finding of this study was that i.v. lidocaine did not abolish or diminish the brain's response as measured by fMRI to acute noxious electrical stimulation of the forepaw in normal rats. Our preclinical results suggest therefore that lidocaine's analgesic efficacy is unlikely to be through an action on normal physiological pain pathways as has been shown for opioids. In addition, lidocaine was observed to enhance brain responses to acute noxious stimulation which was unexpected because lidocaine is known to block sodium channels and propagation of action potentials. We recently showed that both cocaine and lidocaine cause increases in the intracellular calcium concentration $[Ca^{++}]_i$ in somatosensory cortex and we now propose that lidocaine's ability to increase $[Ca^{++}]_i$ in somatosensory neurons could underlie the enhanced cortical activation to noxious and non-noxious stimulation observed here. The increase in $[Ca^{++}]_i$ in somatosensory cortex by lidocaine may also be relevant for its analgesic effects since studies have proposed a decrease in neuronal calcium currents in somatosensory neurons as the mechanism underlying neuropathic pain.

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