Brain activation in a nonhuman primate model of oxaliplatin-induced peripheral neuropathy: suppression with duloxetine

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Goals
- Behavioral and pharmacological characterization of a nonhuman primate model of oxaliplatin-induced peripheral neuropathy.
- Quantify brain activity in macaques with oxaliplatin-induced cold hypersensitivity.
- Effect of drug treatment on brain activity.

Methods

Nonhuman primate oxaliplatin-induced peripheral neuropathy
Oxaliplatin (5 mg/kg, i.v.) was infused over a 2-hr period in female cynomolgus macaques (SNBL, Japan). A second oxaliplatin infusion was performed 2 weeks after the first oxaliplatin infusion.

Tail immersion test & Pharmacology
The tail 10 cm of the macaque’s tail was immersed in 10°C water. The withdrawal latency, amount of time to withdraw the tail, was recorded in sec. The cut off was 20 sec. The average of these latencies is reported. Three days after oxaliplatin infusion, duloxetine (n = 4), pregabalin (n = 4) and tramadol (n = 3) were administered (30 mg/kg, p.o.) and macaques were tested 1 hour after administration.

Functional Magnetic Resonance Imaging (fMRI)
1) Baseline brain activity was measured before oxaliplatin treatment (intact). Three days after oxaliplatin treatment, brain activity was assessed using a Philips Ingenia 3.0T MRI system. Under anesthesia, a gel pack (10°C or 37°C) was applied to the distal tail. The stimuli were alternately applied to the tail for 30 sec with a 30 sec interval separating each stimulation 40 times.

Pain Assessment
Acute cold hypersensitivity following oxaliplatin treatment
Decreased latency to respond to a cold (10°C) but not neutral (20°C) temperature.

Duloxetine increases tail withdrawal latency; pregabalin and tramadol do not

Brain Activity with fMRI

Brain activity in response to cold: before oxaliplatin treatment

Increased brain activation to 10°C in macaques before oxaliplatin treatment (‘intact’). Increased activation induced pain lattice (PE/PD) and primary somatosensory (SI) cortices and pontine nuclei (PN).

Cold activation of secondary somatosensory cortex (SII) and insular cortex (Ins) in oxaliplatin-infused macaques

Z-scores: duloxetine reduces brain activation in response to cold in oxaliplatin-infused macaques

Z-scores: response to cold vs. oxaliplatin-infused macaques

Symbols and Abbreviations
Cb: cerebellum
PMD: dorsal premotor cortex
Ed: dorsal intertemporal cortex
Ins: insular cortex
Mr: primary motor cortex
PE/PD: PE/PD of the inferior parietal cortex
PN: pontine nuclei
SII: primary somatosensory cortex
SII: secondary somatosensory cortex
STG: superior temporal gyrus
FO: area TFO of the parahippocampal cortex
TGI: temporal pole
V1: primary visual cortex

Conclusions
- A robust, acute cold hypersensitivity emerges following oxaliplatin treatment in the nonhuman primate. Cold hypersensitivity appears to be attenuated by selective drugs (duloxetine) in the nonhuman primate model.
- Oxaliplatin-induced cold hypersensitivity in rats appears to be sensitive to numerous pharmacological agents.
- The nonhuman primate could be used as a screening tool to prioritize compounds for clinical testing.

Differential efficacy between rat and macaque models of oxaliplatin-induced neuropathic pain

Pregabalin does not reduce cold-induced brain activation in oxaliplatin-infused macaques

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