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

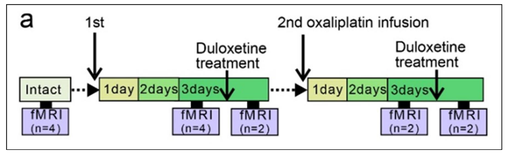
Oxaliplatin (5 mg/kg, i.v.) was infused over a 2 hr. period in female cynomolgus macaques (SNBL, Japan). A second oxaliplatin infusion was performed 2 weeks after the first oxaliplatin infusion.

Tail immersion test & Pharmacology

The distal 10 cm of the macaque's tail was immersed in 10ºC water. The withdrawal latency, amount of time to withdraw the tail, was recorded in sec. The cut off was 20 sec. The average of three 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)

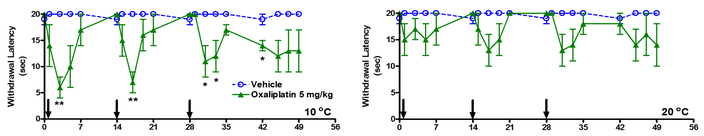
a) Baseline brain activity was measured before oxaliplatin treatment (intact). Three days after oxaliplatin treatment, brain activity was assessed using a Philips Ingena 3.0T MRI system. Under anesthesia, a gel pack (10ºC or 37ºC) was applied to the distal tail. The stimuli were alternately applied to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



The effect of the serotonin-norepinephrine reuptake inhibitor duloxetine and the anticonvulsant pregabalin on brain activity was examined. Baseline brain activity was measured in oxaliplatin-treated macaques (n = 2) and brain activity was measured one hour after drug duloxetine (30 mg/kg, p.o.) administration.

Pain Assessment

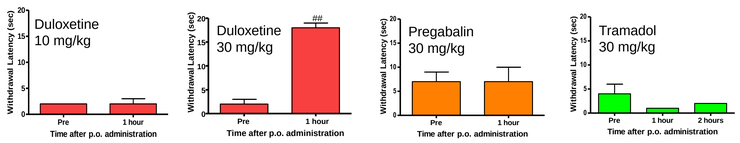
Acute cold hypersensitivity following oxaliplatin treatment



Decreased latency to respond to a cold (10ºC) but not neutral (20ºC) temperature.
↓ Oxaliplatin infusion.

Mean ±SEM, n = 5-6 oxaliplatin-treated, n = 3 vehicle-treated.
*p < 0.05, **p < 0.01 vs. baseline ("0").

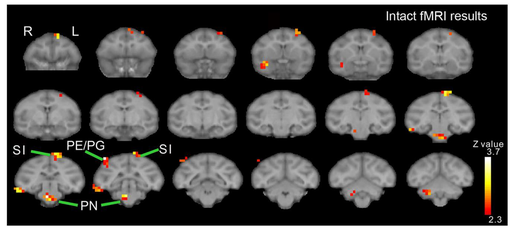
Duloxetine increases tail withdrawal latency; pregabalin and tramadol do not



Mean ± S.E., n = 3～4/Drug ##P < 0.01 vs. Pre

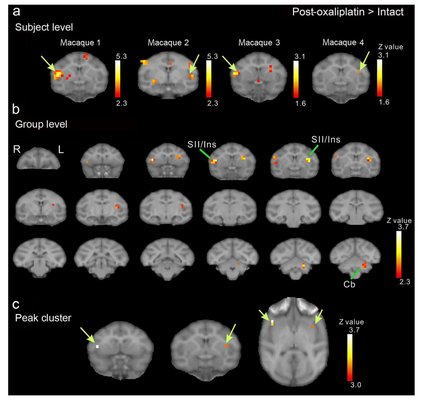
Brain Activity with fMRI

Brain activity in response to cold: before oxaliplatin treatment



Increased brain activation to 10ºC in macaques before oxaliplatin treatment ("intact"). Increased activation induced parietal (PE/PG) and primary somatosensory (SI) cortices and pontine nuclei (PN).

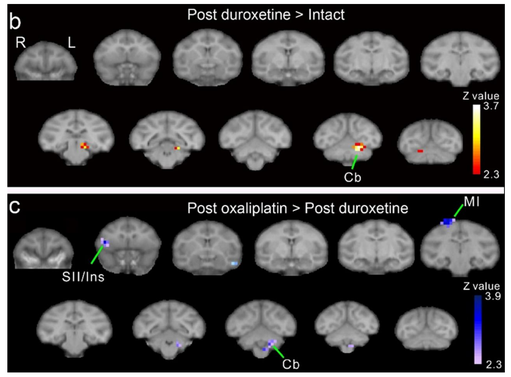
Cold activation of secondary somatosensory cortex (SII) and insular cortex (Ins) in oxaliplatin-infused macaques



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

Area	Hemisphere	Z value	x	y	z (mm)
Intact (10 °C–37 °C)					
PE/PG	Right	3.99	−18	−2	16
PN	Right	3.85	−2	0	−12
SI	Left	3.49	4	2	20
PMd	Left	3.44	4	26	16
	Left	2.99	12	18	16
TEd	Right	3.43	−24	0	−6
TG	Right	3.18	−12	18	−8
Cb	Right	3.04	−8	−10	−12
Post-oxaliplatin (10 °C–37 °C) > Intact (10 °C–37 °C)					
SII/Ins	Right	3.64	−16	20	2
	Left	3.10	14	16	2
Cb	Left	3.04	8	−8	−8

Duloxetine reduces cold-induced brain activation in oxaliplatin-infused macaques



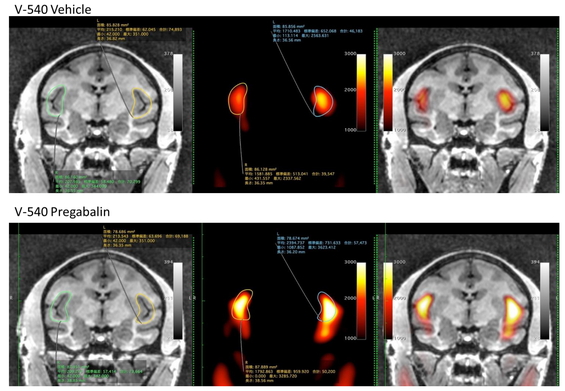
Z-scores: duloxetine reduces brain activation in response to cold in oxaliplatin-infused macaques

Area	Hemisphere	Z value	x	y	z (mm)
After duloxetine treatment (Post-oxaliplatin, 10 °C–37 °C) > Intact (10 °C–37 °C)					
Cb	Left	3.63	8	−12	−6
V1	Left	3.43	−10	24	2
TFO	Left	3.12	8	−2	−6
Before > After duloxetine treatment (Post-oxaliplatin, 10 °C–37 °C)					
STG	Left	3.89	20	20	−10
MI	Right	3.49	−8	4	20
SII/Ins	Right	3.35	−16	22	2
Cb	Left	2.93	6	−8	−12

Symbols and Abbreviations

Cb: cerebellum
PMd: dorsal premotor cortex
Ed: dorsal inferotemporal cortex
Ins: insular cortex
MI: primary motor cortex
PE/PG: PE/PG of the inferior parietal cortex
PN: pontine nuclei
SI: primary somatosensory cortex
SII: secondary somatosensory cortex
STG: superior temporal gyrus
FO: area TFO of the parahippocampal cortex
TG: temporal pole
V1: primary visual cortex

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



Conclusions

- ❑ A robust, acute cold hypersensitivity emerges following oxaliplatin treatment in the nonhuman primate. Cold hypersensitivity appears to be attenuated by select drugs (duloxetine) in the nonhuman primate model.
- ❑ Oxaliplatin-induced cold hypersensitivity in rats appears to be sensitive to numerous of 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

	Rat	Macaque	CIPN clinical trials
Duloxetine	+	+	+
Pregabalin	+	-	-
Tramadol	+	-	?

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