



Neuroimaging of Pain-Related Brain Activation in Nonhuman Primates Pain Models

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PURPOSE

Approximately 20% of the adult population suffer from chronic pain that is inadequately managed with existing analgesics. The lack of effective analgesics stems in part from a lack of appropriate preclinical pain models and from a lack of objective markers that are mechanistically related to pain. The nonhuman primate (NHP) is an ideal preclinical species in that it is neurologically and genetically closer to humans than other preclinical model species. In the current study, pain-related behavior was assessed in NHP models of oxaliplatin-induced neuropathic pain, postoperative pain and in NHP with naturally occurring endometriosis. In addition, brain activity in these pain models was visualized with functional magnetic resonance imaging (fMRI) and analgesics were used to modulate brain activity. Ideally, the current findings would be used not only to further elaborate the mechanism of clinical pain but also to guide the development of clinically useful analgesics.

METHODS

Animals: All cynomolgus macaques used in this study were obtained from SNBL (Japan). Studies were reviewed and approved by the Hamamatsu Pharma Research, Inc. Animal Care and Use Committee.

Naturally-occurring endometriosis (EM) model: Presence of cysts in endometriosis macaques was confirmed with MRI. Immunohistochemical detection of progesterone receptor in ovary was used for diagnosis of endometriosis. Pain assessment was performed as described for the POP model. Antinociceptive efficacy of morphine (6 mg/kg, i.m.) was assessed following measurement of baseline response pressure. For hormonal therapy, macaques with endometriosis were dosed with dienogest (0.05 mg/kg, p.o. BID) for 8 weeks.

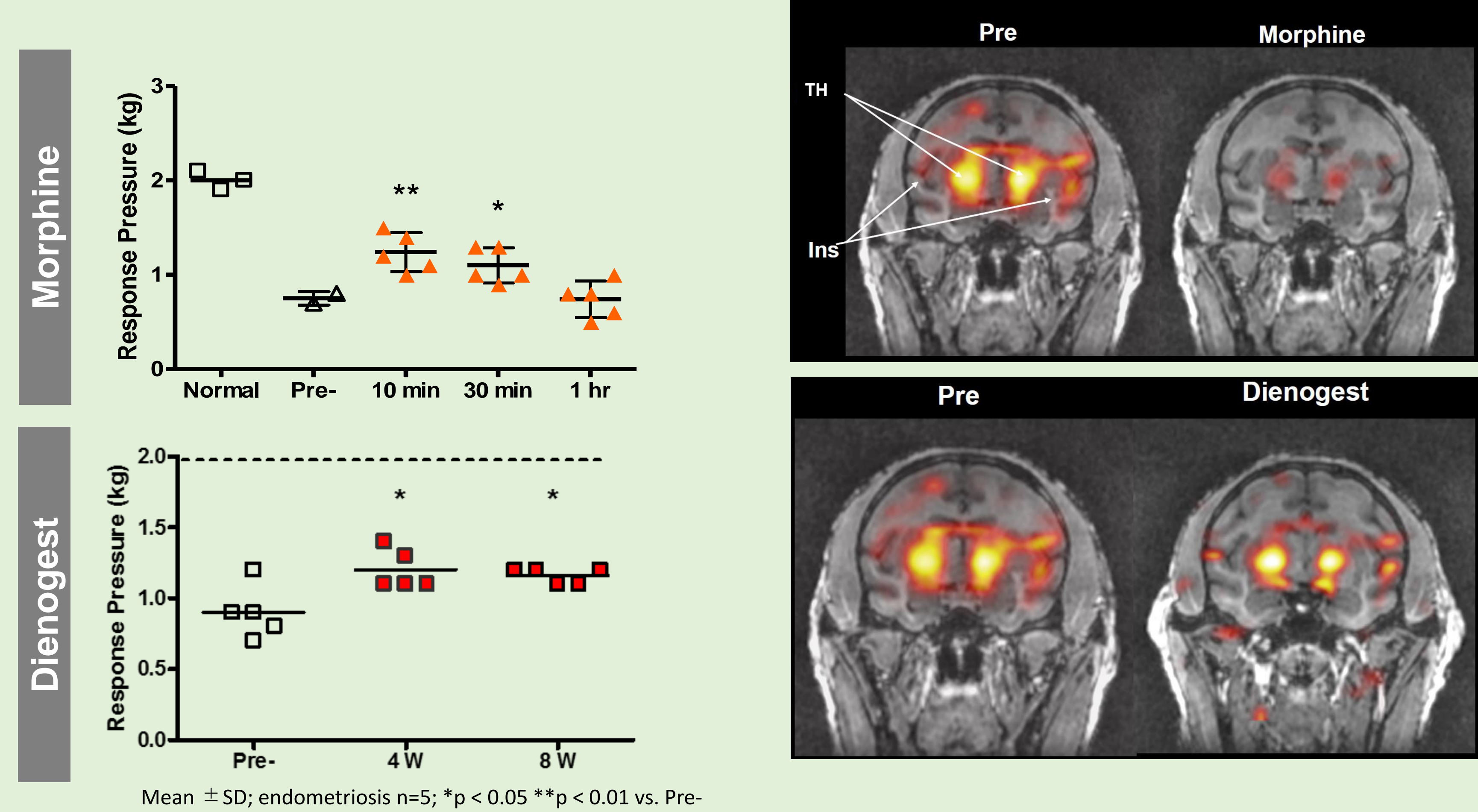
Postoperative pain (POP) model: Under isoflurane anesthesia, a 3 cm long abdominal incision was made through skin and muscle. Postoperative sensitivity to pressure was evaluated proximally and distally (approximately 10 cm) to the surgical site with a pressure algometer. Pressure was applied against the abdomen until tension of the muscle on the top-back of the head (“grimace”) was observed. The average pressure response (kg) was calculated from three measurements. Antinociceptive efficacy of morphine (1-10 mg/kg, i.m.) and pregabalin (3-20 mg/kg, i.m.) was assessed one and two days post-surgery. Following baseline pressure response measurement, drugs were administered once every 30 min. Pressure thresholds were measured 20 min following drug administration.

Oxaliplatin-induced peripheral neuropathy (OXA) model: Oxaliplatin (5 mg/kg, i.v.) was infused over a 2-hr period in female cynomolgus macaques. A second oxaliplatin infusion was performed 2 weeks after the first oxaliplatin infusion. For pain assessment (tail immersion test), the distal 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 three latencies is reported. Three days after oxaliplatin infusion, duloxetine was administered (30 mg/kg, p.o.) and macaques were tested 1 hour after administration.

Brain activity measurement with fMRI: Under propofol anesthesia, brain activity was visualized using a 3.0T MRI Signa HDxt (GE) with an 8-channel head coil. Brain activity was observed before and during either application of a cold stimulus to the tail (OXA model) or abdominal pressure with a 1-kg weight (POP, EM models). In addition, the effects of analgesic drugs on brain activity during stimulation were observed.

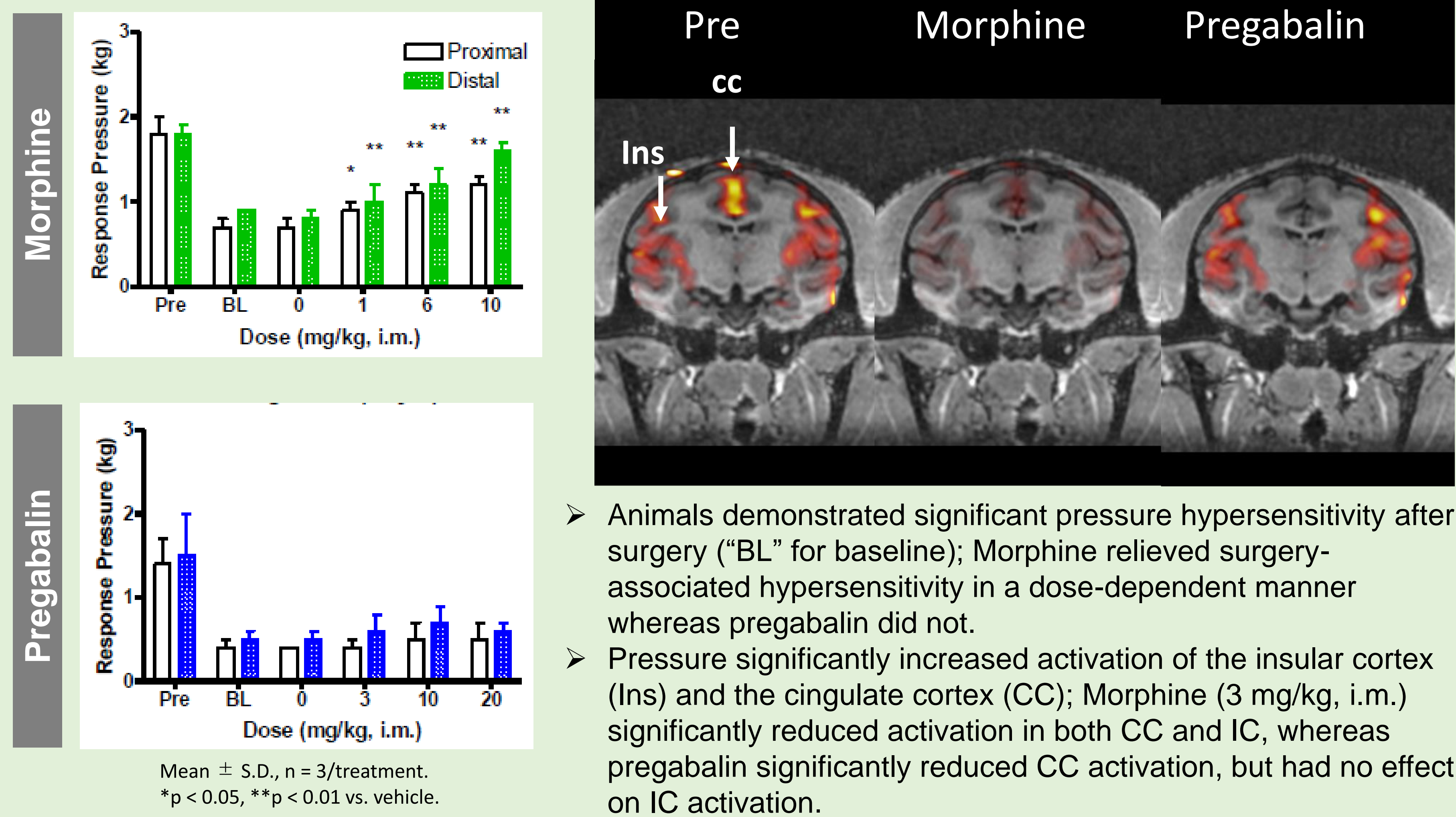
RESULT

Endometriosis Model



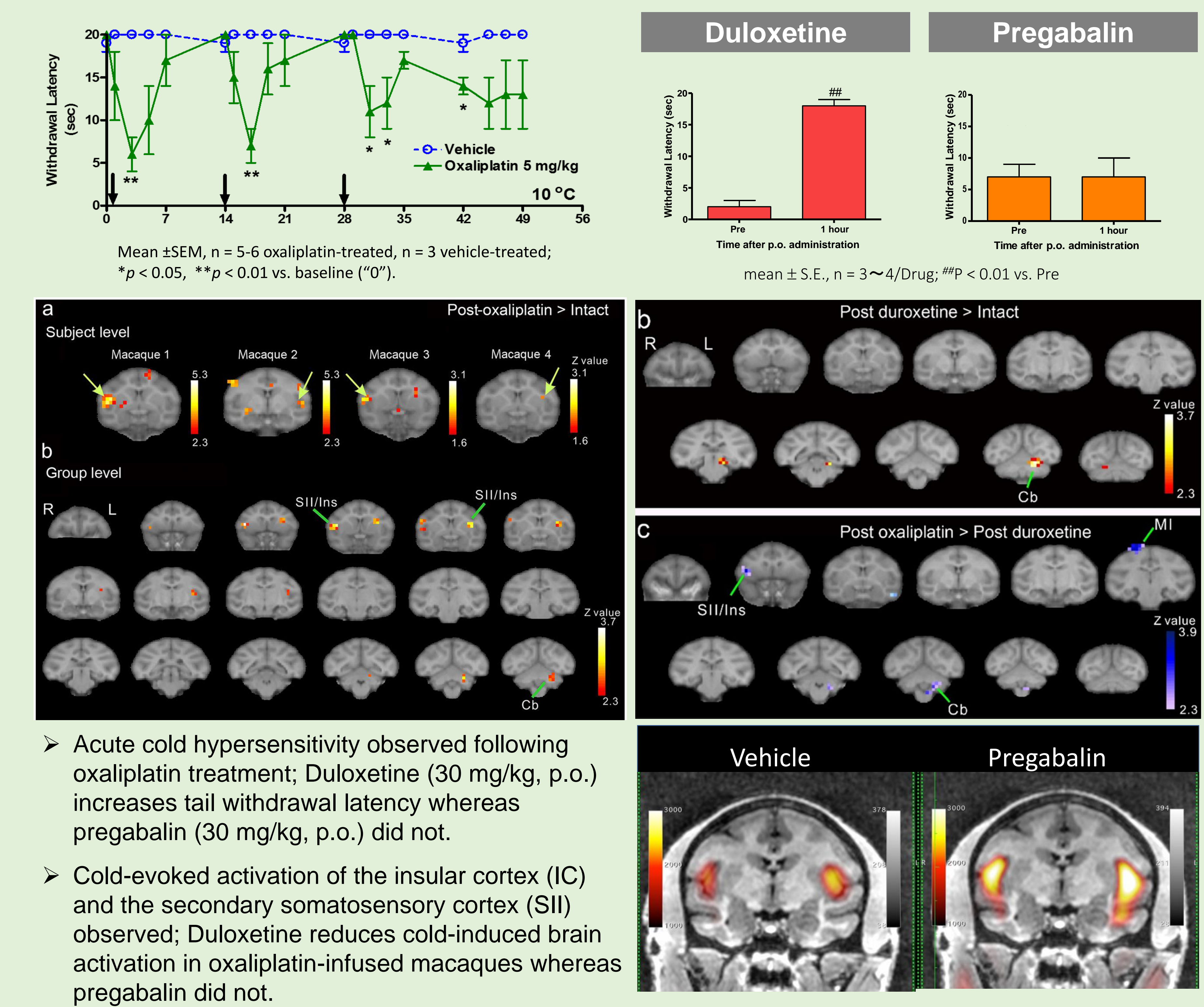
- Animals with endometriosis demonstrated significant pressure hypersensitivity.; Morphine and dienogest relieved endometriosis-associated hypersensitivity.
- Pressure significantly increased activation of the insular cortex (Ins) and the thalamus (TH); Morphine (3 mg/kg, i.m.) attenuated pressure-induced activation of Ins and BG; Eight-week treatment with dienogest (0.05 mg/kg, p.o., BID) attenuated pressure-induced brain activation.

Postoperative Pain Model



- Animals demonstrated significant pressure hypersensitivity after surgery (“BL” for baseline); Morphine relieved surgery-associated hypersensitivity in a dose-dependent manner whereas pregabalin did not.
- Pressure significantly increased activation of the insular cortex (Ins) and the cingulate cortex (CC); Morphine (3 mg/kg, i.m.) significantly reduced activation in both CC and IC, whereas pregabalin significantly reduced CC activation, but had no effect on IC activation.

Oxaliplatin-Induced Peripheral Neuropathy Model



- Acute cold hypersensitivity observed following oxaliplatin treatment; Duloxetine (30 mg/kg, p.o.) increases tail withdrawal latency whereas pregabalin (30 mg/kg, p.o.) did not.
- Cold-evoked activation of the insular cortex (IC) and the secondary somatosensory cortex (SII) observed; Duloxetine reduces cold-induced brain activation in oxaliplatin-infused macaques whereas pregabalin did not.

CONCLUSIONS

- ❑ Activation of unique as well as common brain areas appears across NHP pain models and appears to be related to pain. Thus, NHP brain activation could be used as an objective, preclinical marker of pain for various pain states.
- ❑ The current findings also indicate that increased brain activation can be pharmacologically modulated.
- ❑ Brain imaging could also be used as an objective, preclinical marker to guide the development of analgesic drugs and potentially “screen-out” non-analgesic drugs.

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