Brain activation and suppression with morphine in a nonhuman primate model of postoperative pain

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Goals

- ❑ **Behavioral and pharmacological characterization of a nonhuman primate model of postoperative pain.**
- ❑ **Postoperative pain brain activation.**
- ❑ **Pharmacological manipulation of brain activation.**

Methods

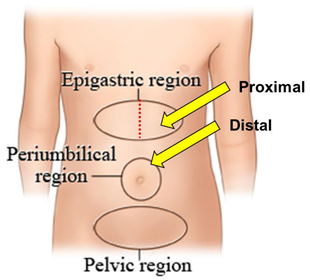
Subjects:

Cynomolgus macaques, 2-4 kg (SNBL, Japan).

Macaques were tested before surgery and once daily beginning 24 hours following surgery.

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. The macaque was restrained in a monkey chair and an algometer was pushed 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.

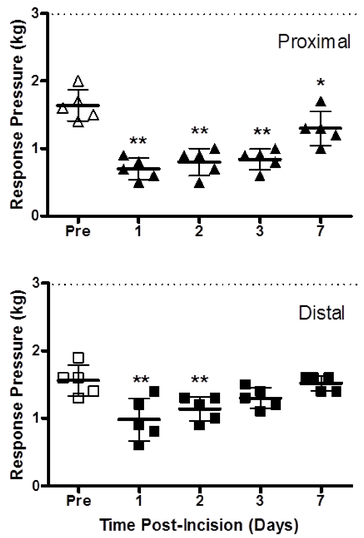


Antinociceptive efficacy of clinically used analgesics was assessed one and two days post-surgery. To utilize the least number of macaques, a cumulative dosing protocol was used to test drug efficacy. Following baseline pressure response measurement, drugs were administered once every 30 min. Pressure thresholds were measured 20 min following drug administration.

Brain activity was measured with functional magnetic resonance imaging (Signa EXCITE HDxt 3.0T, GE Healthcare). A 1 kg weight applied near the surgical site was used to evoke brain activation. Following acquisition of baseline responses to pressure, either morphine (6 mg/kg) or pregabalin (20 mg/kg) was administered (i.m.).

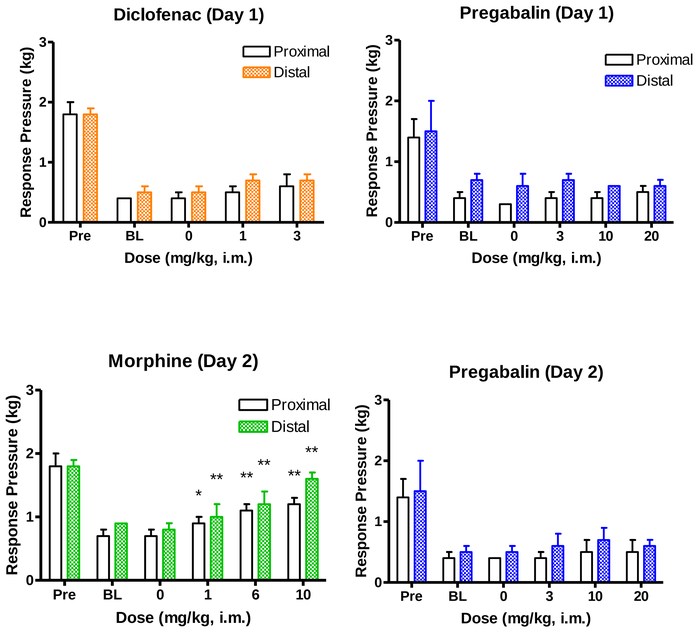
Pain Assessment

Postoperative hypersensitivity: time course



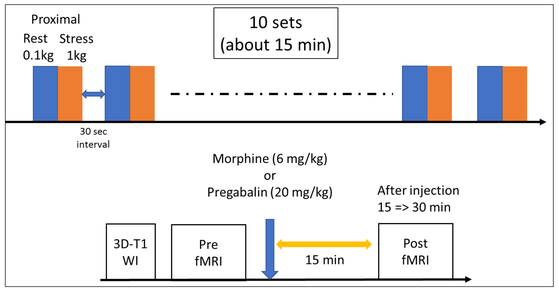
Beginning 1 day following abdominal surgery, macaques demonstrated significantly decreased pressure response thresholds, both proximally and distally to the surgical site compared to pre-surgical baseline ("Pre"). Recovery to near normal thresholds were observed one week following surgery. Mean ± S.D., n = 5. *p < 0.05, **p < 0.01 vs. "Pre".

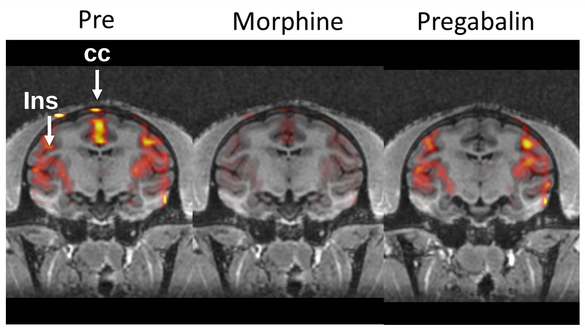
Antinociceptive efficacy



Effect of analgesic drugs on postoperative pain. Response pressure was measured before ("Pre") and one and two days after surgery. After baseline ("BL") response pressure measurement, macaques were i.m. dosed with vehicle ("0"), followed by cumulative doses of diclofenac, morphine and pregabalin. Mean ± S.D., n = 3/treatment. *p < 0.05, **p < 0.01 vs. vehicle.

fMRI





CC, cingulate cortex; Ins, insular cortex

Summary

- ❑ Robust proximal and distal postoperative pressure hypersensitivity in macaques.
- ❑ Postoperative hypersensitivity relatively short-lasting.
- ❑ Activation of cingulate and insular cortex could be related to postoperative pain.
- ❑ Lack of pregabalin efficacy in the macaque compared to the rat: possibly due to an underlying species-specific neurological mechanism.

Potential differential efficacy: rat vs. macaque

Drug	Rat hind paw incision	NHP abdominal incision
Morphine	Yes	Yes
Diclofenac	No MTD: 10 mpk, p.o.	No MTD: 3 mpk, i.m.
Pregabalin	Yes	No MTD: 20 mpk, i.m.

MTD, maximum tested dose.

Conclusions

- ❑ **The macaque model could be used to better understand mechanism of clinical postoperative pain.**
- ❑ **Macaque brain activity could be used to predict efficacy of novel therapeutics.**
- ❑ **Differential brain activation between pain states suggests a need for pain-specific analgesics.**

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