Enzyme inhibitors of NOS and FAAH are antinociceptive in a rat model of peripheral neuropathic pain

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BACKGROUND

- Nitric oxide (NO) is a free radical gas that acts as a cellular messenger in the CNS and PNS
- Neuronal nitric oxide synthase (nNOS) is located in the spinal cord dorsal horn and in dorsal root ganglion (DRG) cells
- Peripheral nerve injury increases nNOS-i.r. in the ipsilateral L4-L6 DRGs and spinal dorsal horn
- Currently available so-called selective nNOS inhibitors are only marginally selective
- This study aimed at evaluating the effectiveness of a novel highly selective nNOS inhibitor in a cuff-induced animal model of neuropathic pain
- Fatty acid amide hydrolase (FAAH) metabolises fatty acid amides and stimulates inducible nitric oxide synthase
- This study also evaluated the effectiveness of an inhibitor of FAAH in this model.

METHODS

Subjects: male Sprague Dawley rats, 250-350 g

Model: (Mosconi & Kruger, Pain 1996):
- left sciatic nerve exposed under anaesthesia
- cuff placed around nerve (2 mm PE-90 tubing)

Sensory testing:
- von Frey test of tactile hypersensitivity
- incapacitance test of preferential hind paw weight distribution
- height/cold place preference test & cold hypersensitivity

Drugs tested:
- 7-nitroindazole (7-NI) – nNOS inhibitor
- NeurAxon compound 323 (NXN 323) – selective nNOS inhibitor
- OL-135 – fatty acid amide hydrolase inhibitor

Statistical Analysis:
- One-way or mixed two-way ANOVA followed by Tukey’s HSD for post hoc comparisons

RESULTS

FIG. 1 – Effects of 7-NI (30 mg/kg, i.p.) on tactile hypersensitivity in the NeP rat in the von Frey test

Results:
- in NeP rats hind paw withdrawal threshold was < 5 g
- 30 min after 7-NI admin. no difference in withdrawal threshold
- 60 min after 7-NI admin. threshold was significantly higher than before drug administration

FIG. 2. Effect of NXN 323 vs. vehicle on tactile hypersensitivity in NeP rats in the von Frey test

Results:
- 9 days after model induction acute admin. of NXN 323 reversed tactile hypersensitivity when tested at 1, 2 and 24 hours

FIG. 3. Effect of daily administration of NXN 323 over our days to NeP rats in the von Frey test

Results:
- effect of acute injection of NXN 323 was similar on each of the 4 successive days
- withdrawal threshold recovered to the same level after each of the four administrations

FIG. 4. Mean effect of NXN 323 given daily over four days on tactile hypersensitivity in the von Frey test

FIG. 5. Effect of a single acute administration of NXN 323 (30 mg/kg, i.p.) in the incapacitance test

Results:
- NeP rats show a preferential weight distribution on contralateral hind leg
- NXN normalizes weight distribution in NeP rats

FIG. 6. Effect of four daily acute administrations of NXN 323 in the incapacitance test

Results:
- NXN 323 shifted weight distribution toward control at 2 and 4 hours after admin.
- after 24 hours distribution of weight was preferentially on the contralateral hind leg

FIG. 7. Effects of NXN 323 on place preference in the elevated/cold platform preference test

Results:
- NeP rats demonstrated significantly greater time in the open platform than naïve controls
- cold hypersensitivity
- NXN 323 partially reversed cold hypersensitivity

FIG. 8. Effect of repeated daily doses of NXN 323 on frequency of paw lifting behaviour on the cold platform

Results:
- NeP but not control rats display paw lifts on the cold platform
- NXN 323 decreases paw lifts to approx. 9

FIG. 9. Effect of the FAAH inhibitor OL-135 in the von Frey test

Conclusions:
- OL-135 reversed the tactile hypersensitivity in the von Frey test

NOTES

Mosconi T, Kruger L. Tridentinamide polyethylenes are effective in the rat acute nerve injury-induced pain model. Ultrastructural morphometric analysis of sciatic abnormalities. Pain 84, 275-1, 1999


CONCLUSIONS

1. nNOS inhibitors, 7-NI and NXN 323, reduce tactile & cold hypersensitivity in the cuff model of neuropathic pain in the rat
2. NXN 323 acutely reverses the preferential hind paw weight distribution in the incapacity test
3. repeated daily administration of NXN 323 does not demonstrate increasing or decreasing effectiveness
4. effects of NXN 323 are maximum at 2 and 4 hours after administration
5. the FAAH inhibitor, OL-135, reduces tactile hypersensitivity in the von Frey test
6. the results suggest that NXN 323 may prove to be effective in reducing the pain of peripheral neuropathy