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Targeting cgrp via receptor antagonism and antibody neutralisation in two distinct rodent models of migraine-like pain

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AIM

To evaluate the involvement of CGRP in two distinct rodent models of migraine: The glyceryl trinitrate (GTN) mouse model and the spontanous trigeminal allodynia (STA) model using a monoclonal CGRP antibody (ALD405) and a receptor antagonist (olcegepant).

CONCLUSION

We show that CGRP is critically involved in both GTN induced hyperalgesia in mice and in the STA rat model of migraine emphasizing the clinical relevance of the two models. Moreover, the unexpected rapidity of onset observed for ALD405 supports a probable site of action outside the blood-brain barrier.

RESULTS

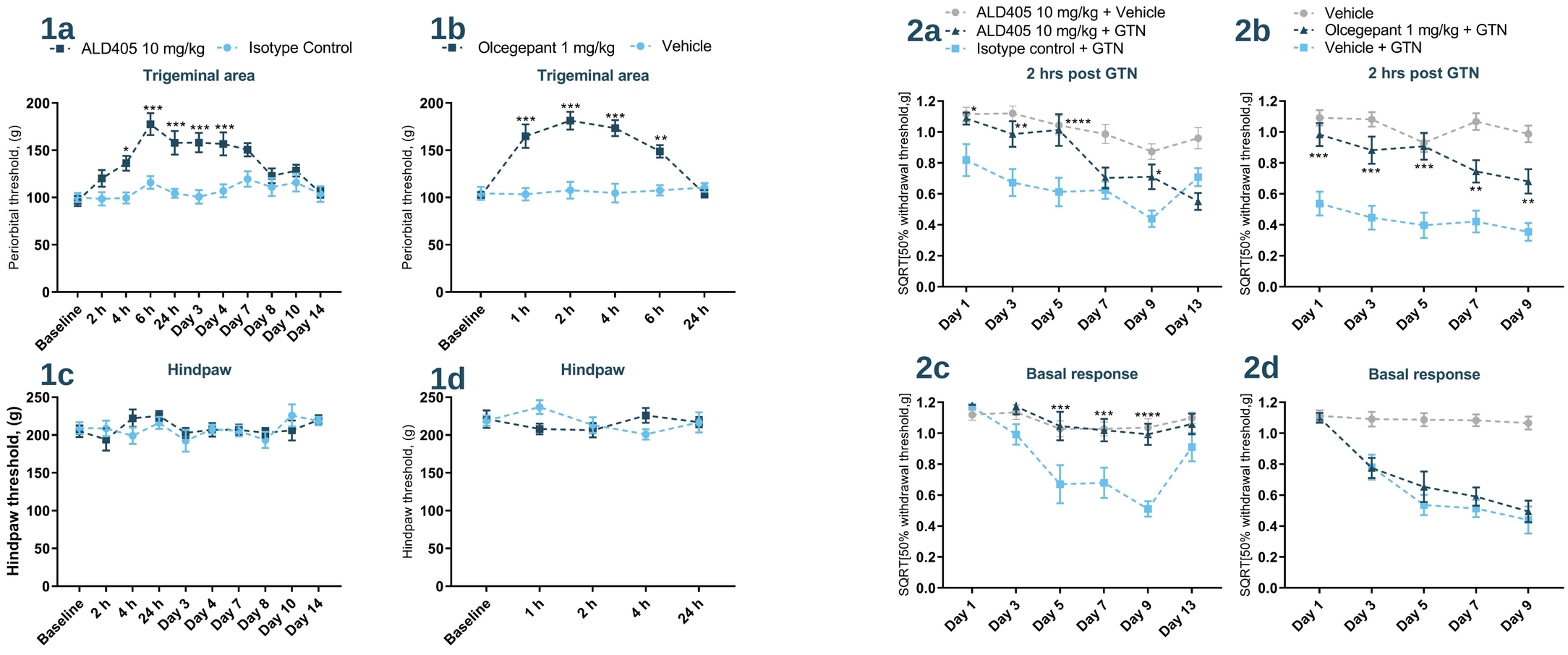
SPONTANOUS ALLODYNIA RAT MODEL

Both ALD405, fig. 1a and olcegepant, fig. 1b effectively alleviated periorbital hyperalgesia in the STA rats. Hindpaw mechanical thresholds were unaffected by both ALD405 and olocegepant, fig 1c and 1d respectively.

GTN MOUSE MODEL

Figure 2a and 2b show that both ALD405 and olcegepant significantly alleviated acute GTN induced hyperalgesia compared to the IgG isotype control and vehicle treatments. Olcegepant could not prevent the progression of GTN mice into a basal hyperalgesic state, fig. 2d whereas ALD405 completely inhibited this, fig. 2c.

In both models distinct pharmacokinetic profiles of the ALD405 and olcegepant were evident as a single injection of ALD405 was effective for 6-7 seven days and olcegepant was acutely effective.



METHODS

SPONTANOUS ALLODYNIA RAT MODEL

The STA rat strain is a unique inbred strain presenting with cephalic hyperalgesia to mechanical stimulation, but with normal sensitivity in peripheral pain circuits. After baseline measurements STA rats were dosed with ALD405 10 mg/kg, i.p and periorbital and hind paw sensitivity assessed for 14 days, n=10. Olcegepant was administered 1 mg/kg, i.p. and rats followed for 24 hrs, n=10. An electronic von Frey device (IITC Life Science Inc) was used to measure mechanical sensitivity.

GTN MOUSE MODEL

GTN 10 mg/kg was administered i.p. every other day after baseline measurement (basal response) of hind paw sensitivity to stimulation with von Frey filaments (Ugo Basile). ALD405 10 mg/kg was administered as a single i.p. injection the day before starting GTN provocations. Olcegepant 1 mg/kg, i.p. was given 15 min. prior to GTN on every test day. Acute response to GTN was obtained 2 hrs. after injection. Group size 10-12.

Rat and mouse data were analysed with a two-way repeated measure ANOVA and Bonferroni's post hoc test.

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