Differential effects of sumatriptan, administered pre- and post-sensitisation, on spontaneous activity and mechanical responses of trigeminal neurones in three rat models of migraine

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❶ INTRODUCTION

Migraine is a common clinical condition affecting about one fifth of the general population. The use of animal models have provided substantial advances in our understanding of the mechanisms underlying migraine attacks, as well as the development of specific therapeutic agents. Three rat models of migraine, monitoring sensitization of trigeminal neurones, induced by dural application of capsaicin, inflammatory soup (IS) and intravenous infusion of glycerol trinitrate (GTN), a nitric oxide donor, are frequently employed. However, few studies have been carried out to compare these three models in terms of their neuronal properties and their responses to treatments. The objectives of the study were to investigate the differences in electrophysiological properties and responses to mechanical stimulation of trigeminal nucleus caudalis (TNC) neurons and effects of sumatriptan, a 5-HT 1B and 1D receptor agonist, administered pre-emptively or post-induction of sensitization, in these three models.

❷METHODS

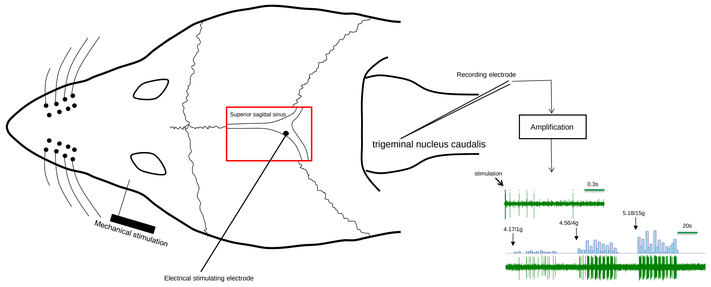


Fig. 1. Diagram showing extracellular recording from trigeminal nucleus caudalis (TNC) neurones and examples of responses to electrical and mechanical stimulation on superior sagittal sinus.

Male SD adult rats (300-450g) were anaesthetized with urethane (1.2 g/kg i.p.). A laminectomy at C1-C2 level was made to expose the TNC. A craniotomy was made to allow access to the transverse sinus and superior sagittal sinus for stimulation with irritants. The animals were artificially ventilated throughout the experiment. Extracellular unitary recordings were carried out to monitor spontaneous firing and responses of wide dynamic range (WDR) neurones of the TNC to mechanical stimulation, with three von Frey hairs (4.17/1g, 4.56/4g and 5.18/15g) applied on the facial receptive field. Three migraine models were induced as follows:

Model I: 1% Capsaicin 30 μl on dura;

Model II: IS (containing 1 mM histamine, 1 mM serotonin, 1 mM bradykinin and 0.1 mM prostaglandin E2), 30μl on dura;

Model III: GTN 10 μg/ml 3.0 ml in saline, systematically infused for 15-30 mins.

Sumatriptan, at a dose of (1 mg/kg), was intravenously administered before (pre-emptively) or after (post-induction) the application of above the irritants.

❸RESULTS

Model I: 1% Capsaicin

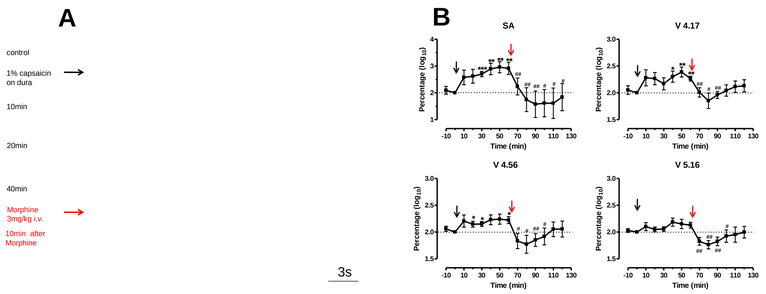


Fig. 2. **A**: An example of recording traces to show increased spontaneous activity (SA) of a WDR neurone of TNC induced by capsaicin on to the dura. **B**: Pooled data showing increased SA rate (in %) relative to that at 0 min and mechanically induced responses of WDR neurones of TNC induced by 1% capsaicin on dura (n=6). V4.17, V4.56 and V5.16 representing von Frey hairs 4.17/1g, 4.56/4g and 5.16/15g. Black arrow: capsaicin on dura; Red arrow: morphine 3 mg/kg i.v. *, **, ***: P<0.05, 0.01, 0.001, respectively, compared to 0 min, paired Student's t-test; #, ##, ###: P<0.05, 0.01, 0.001, respectively, compared to 60 min, paired Student's t-test.

Model II: inflammatory soup (IS)

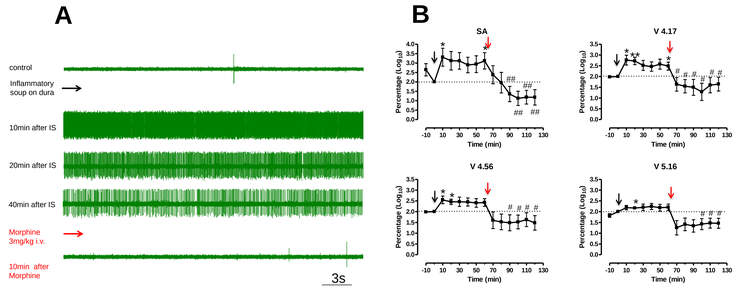


Fig. 3. **A**: An example of recording traces to show increased spontaneous activity (SA) of a WDR neuron of TNC induced by inflammatory soup (IS) on to the dura. **B**: Pooled data showing increased SA rate (in %) relative to that at 0 min and mechanically induced responses of WDR neurones of TNC induced by von Frey hairs (n=6). V4.17, V4.56 and V5.16 representing von Frey hairs 4.17/1g, 4.56/4g and 5.16/15g. Black arrow: IS on dura; Red arrow: morphine 3 mg/kg i.v. *, P<0.05, compared to 0 min, paired Student's *t*-test; #: $P < 0.05$ and 0.01, respectively, compared to 60 min, paired Student's *t*-test.

Model III: Glycerol Trinitrate (GTN)

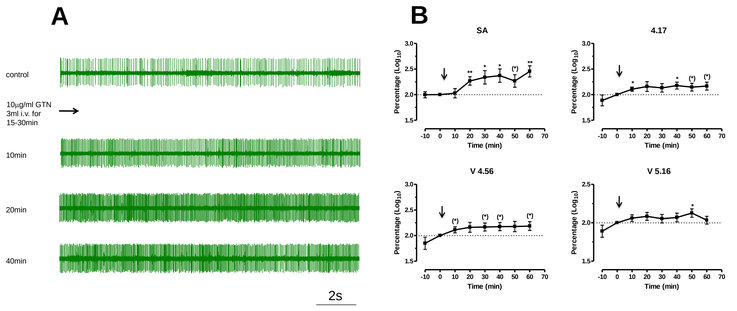


Fig. 4. **A**: An example to show increased spontaneous activity (SA) of a WDR neurone of the TNC induced by GTN infusion. **B**: Pooled data showing increased SA (in %) of WDR neurones of the TNC induced by intravenous infusion of GTN (n=12) and von Frey hair-induced responses, all % relative to the rate at 0 min. V4.17/1g, 4.56/4g and 5.16/15g: von Frey hairs 4.17/1g, 4.56/4g and 5.16/15g, respectively. Black arrow: 10 μg/ml glyceryl trinitrate (GTN) 3 ml infused in for 15-30min; *, **: P < 0.05 and 0.01, respectively; (*): 0.05 < P < 0.1, compared to 0 min, paired Student's *t*-test.

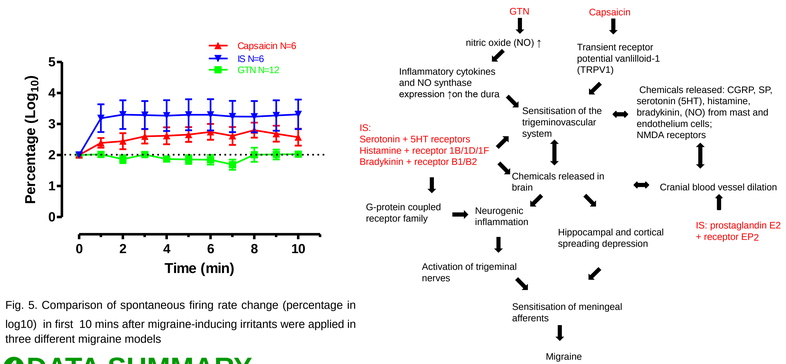


Fig. 5. Comparison of spontaneous firing rate change (percentage in log10) in first 10 mins after migraine-inducing irritants were applied in three different migraine models

❹DATA SUMMARY

In all three migraine models, spontaneous activity and responses of WDR neurones to mechanical stimulations increased significantly. The effects of capsaicin and IS in sensitising TNC neurones were observed after a short delay (<10 min), while GNT-induced effects were with a significant delay (up to 20 min). Pre-emptive application of sumatriptan significantly prevented the sensitisation of TNC neurones in all three models. Application of sumatriptan after the sensitisation was established led to inhibition of the increased spontaneous activity and mechanical responses in the GTN model but not in the capsaicin and IS models.

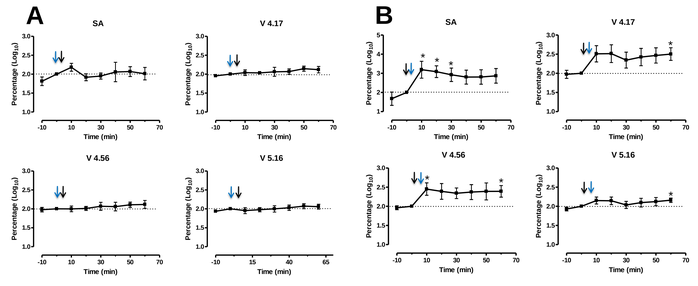


Fig. 6. Effects of 1 mg/kg sumatriptan i.v. pre-emptively (**A**) or post-induction of sensitization (**B**) on spontaneous activity (SA) and mechanically induced responses of WDR neurones of TNC in migraine model induced by capsaicin application on to the dura (n=6 for each group). V4.17, V4.56 and V5.16 representing von Frey hairs 4.17/1g, 4.56/4g and 5.16/15g. Blue arrow: time for sumatriptan 1 mg/kg, i.v.; Black arrow: time for capsaicin on to the dura. *: $P < 0.05$, compared to 0 min, paired Student's *t*-test,

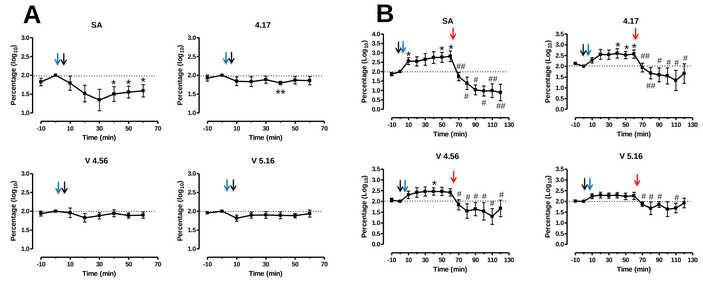


Fig. 7. Effects of sumatriptan1 mg/kg, i.v., pre-emptively (**A**) or post-sensitization (**B**) on spontaneous activity (SA) and mechanically induced responses of WDR neurones of TNC in migraine model induced by IS on dura (n=7 for A and n=6 for B). V4.17, V4.56 and V5.16 representing von Frey hairs 4.17/1g, 4.56/4g and 5.16/15g. Blue arrow: time of sumatriptan injection; Black arrow: time of capsaicin application; Red arrow: time for morphine (3mg/kg) injection. *: $P < 0.05$, compared to 0 min time point. #, ##: $P < 0.05$ and 0.01, respectively, compared to 60 min time point.

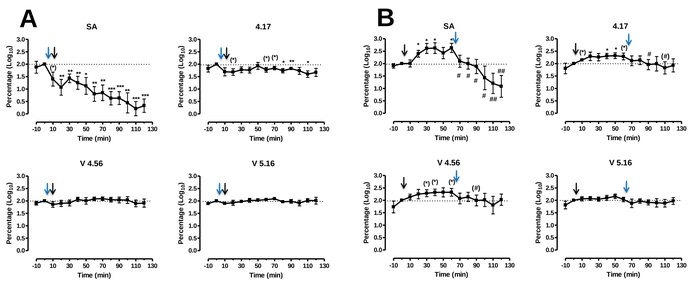


Fig. 8. Effects of sumatriptan,1 mg/kg i.v. pre-emptively (**A**) or post-sensitization (**B**) on spontaneous activity (SA) and mechanically induced responses of WDR neurones of TNC in migraine model induced by GTN infusion. v4.17/1g, 4.56/4g and 5.16/15g: Von Frey hairs with the labelled forces. Black arrow: GTN application; Blue arrow: sumatriptan administration. *, **, ***: P<0.05, 0.01 and 0.001, respectively, paired student's *t*-test compared to 0 min time point; (*), 0.05 < P < 0.1. #: paired student's *t*-test with 60min; #, ##: P<0.05 and 0.01, respectively; (#), 0.05 < P <0.1.

❺CONCLUSION

Our data suggests some common mechanisms may underlie the sensitisation of TNC neurones in three migraine models. However, the difference in induction time in sensitising TNC neurones and different effects of sumatriptan in these models suggest that some subtle differences in the mechanisms of migraine may exist in different models and this needs to be addressed when using these models for the development of therapeutic agents.

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