Characterization of the mouse model of chloroquine-induced pruritus using an automated recording system

Gema Tarrasón, Carla Carcasona, Peter Eichhorn, Adelina Orellana, Richard Roberts, Núria Godessart, Amadeu Gavaldà

Almirall R&D Center, Barcelona Spain

Introduction

Pruritus is the most common symptom of many dermatological indications and has a large unmet medical need. Current treatments are based on first-generation anti-histamines and off-label use of analgesic and antidepressant drugs, which have limited efficacy.

Itch induced by the antimalarial drug chloroquine (CQ) has been used in mice as a translational model of pruritus.

In pruritus models, scratching is usually evaluated from video-recording and manual counting. This method has two limitations; it is time-consuming and it cannot distinguish pruritus inhibition due to an antipruritic effect or to a CNS effect.

Our aim has been to further characterize the CQ model and explore its utility for the screening of drugs using an automated recording system (Laboras, Metris).

Materials & Methods

Chloroquine induced pruritus model in mice

Pruritus was induced by subcutaneous (s.c.) injection of chloroquine at 8, 16, 32mg/kg (corresponding to 200, 400 and 800μg/mice) or oral route at 100mg/kg to adult male C57BL/6.

To evaluate the antipruritic efficacy of the compounds, pruritus was induced by subcutaneous injection of chloroquine at 16mg/kg.

Compounds or vehicle (0.5% methylcellulose + 0.1% Tween 80 in water) were administrated by intraperitoneal (i.p) or oral (po) route 30 or 45 minutes before chloroquine challenge.

The scratching bouts were counted during 30 minutes after chloroquine challenge. Manual and/or automated recording system (Laboras, Metris) were used to measure scratching and spontaneous locomotion activity.

Scratching and locomotor activities quantification LABORAS is a validated and non-invasive technology based on vibration and force signal analysis to determine both the behaviour and the position of the animal along the apparatus. Each behaviour has its own unique signature of signal characteristics which can be detected by the software to identify a behaviour, e.g. scratching and locomotion.

Quantification of CQ tissue levels CQ plasma levels were determined by UPLC-MS/MS after protein precipitation. Brains were homogenized with methanol (1:4, v/v), sonicated and the supernatants analysed by UPLC-MS/MS. Skin samples were extracted with acetonitrile/0.3%TF. A fastPrep analysis on Waters Xvevo.

Effect of Naloxone on CQ induced pruritus

As reported, oral Naloxone induces a dose-dependent inhibition of scratching.

Only low doses of Naloxone inhibit scratching with minor reduction of spontaneous locomotor activity.

The combined recording of scratching and locomotor activity reveals the potential therapeutic margin of the drug.

References

- Liu et al., 2009 Sensory neurons-specific GPCR Mrgprs are itch receptors mediating chloroquine-induced pruritus, Cell 139: 1253-1265

Acknowledgements

The authors would like to acknowledge Laia Benevant, Joan Marfà, Luís Boix, Jose Luis Gómez and Mami de Luca for their technical assistance.

Conclusion

The combined recording of scratching and locomotor activity in an automated system not only increases the throughput of the model but also allows to discriminate between efficacy and CNS effects of the tested drugs.