Different Interpretation of the Hot Plate Test in Rats

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ABSTRACT

Thermal tests have been widely used in rodents; one of the main models used is the hotplate test. Classically the hotplate test has been used as an indication of analgesia using 52.5^{o}C as the thermal stimulus (South, S.M. 2009). With the development of new targets for pharmacotherapy some concern has orison over disruption of thermal perception (eg TRPV1). Thus, we would like to propose that the hotplate can provide a useful tool to address these concerns pre-clinically when it is used at higher temperatures and can be useful in the detection of impairment to temperature perception. In the present study, pharmacology was assessed using a TRPV1 antagonist (PF-3864086, PF-386). TRPV1 antagonists have been reported to have effects on thermal perception. These effects have been highlighted in clinical studies, namely arm emersion and hot water sipping test (ASCPT March 2009). PF-386 has a similar profile to the MK2295 published clinically and is utilised in this study.

Animals were acclimatised to the hotplate (Ugo Basile) prior to testing (at 48^{o}C, a non-noxious temperature). Animals were then assessed over a range of temperatures (50^{o}C, 52.5^{o}C + 55^{o}C) on consecutive days in the same batch of animals, i.e. 50^{o}c day 1, 52.5^{o}C day 2 and 55^{o}C on day 3. Animals were placed on the hotplate and latency to respond was recorded in seconds (flinching, licking, biting or jumping). Baseline responses were taken on each test day to establish normal responses at a given temperature prior to pharmacological evaluation. PF-386 was assessed at 100+300mg/kg p.o. tested 1 +3hrs post dosing.

Results show that 100mg/kg significantly increased latency to respond at 52.5^{o}C and 300mg/kg at 50^{o}C, 52.5^{o}C and 55^{o}C.

These results indicate that there is impairment to thermal perception at these doses; the lack of effect with 100mg/kg at 55^{o}C could be due to other TRP channels being activated at this higher temperature which are blocked only by the 300mg/kg dose. The data aligns with clinical data indicating that potential safety risks can be detected with this model. This model could be a useful translatable biomarker which could be extended to projects beyond TRPV1, to determine changes to normal thermal perception.

Author Keywords

Hot plate, rat, TRPV1, thermal perception.

Ethical Statement

Experiments were conducted on male Sprague Dawley rats (175-200g) from Charles River UK. Animals were housed in 4s, maintained on a 12/ 12-h light/dark cycle with food and water available *ad libitum*. All procedures were performed in accordance with the UK Animals (Scientific Procedures) Act 1986.

REFERENCES

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