Inhibition of Airway Hyperresponsiveness by TRPV1 Antagonist (SB-705498)[1] in Sensitised Guinea-Pig Using Plethysmography

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Airway sensory nerves play a key role in respiratory cough, dyspnoea, airway hyperresponsiveness (AHR), all fundamental features of airway diseases (asthma and COPD). Vagally-mediated airway reflexes such as cough, bronchoconstriction and chest tightness originate from stimulation of airway sensory nerve endings. The transient receptor potential vanilloid 1 receptor (TRPV1) is present on peripheral terminals of airway sensory nerves and modulation of its activity represents a potential target for the pharmacological therapy of AHR in airway disease.

Conscious male Dunkin-Hartley guinea-pigs (300-350g), sensitised with ovalbumin (OA) (100µg mL^{-1} aluminium hydroxide (13mg mL^{-1}) i.p.) on day 0 and day 7, were restrained in double chamber plethysmography boxes on day 21. Specific airway conductance (sGaw) was derived from the airflow and calculated as % of change from baseline. Saline (0.9% w/v NaCl) was nebulised for habituation of the guinea-pigs. SB-705498 10mg kg^{-1} and methylcellulose 1mL kg^{-1} were evaluated p.o in 2 different studies. In the 1st study, control (n=11) and treated (n=8) animals were dosed 1h before OA (10min aerosol of 1mg mL^{-1}) induced bronchoconstriction; then 2h30 after dosing, OA evoked AHR to histamine was evaluated with a previously subthreshold dose of histamine (0.03mg mL^{-1}). In the 2nd study, control (n=7) and treated (n=8) animals were dosed 1h before histamine (0.1mg mL^{-1})-evoked bronchoconstriction. sGaw area under the curve (AUC) was analysed. Statistical comparisons were performed using ANOVA. Values of $p<0.05$ were considered significant.

sGaw is one of the major parameters used in clinic to measure airway tone. SB-705498 did not have any effect on OA-evoked bronchoconstriction. However, SB-705498 caused a significant ($P<0.05$) inhibition of OA-evoked AHR to histamine. In separate experiments this effect of SB-705498 was shown not to be due to antihistamine effects.

The TRPV1 antagonist, SB-705498 produced significant inhibition of OA-evoked AHR to histamine in OA-sensitised, conscious guinea-pigs using a double chamber plethysmography model. Furthermore, this effect was not related to histamine-antagonist activity. These data suggest that TRPV1 receptors located on airway sensory nerves may be important in the development of AHR.

[1]Rami, HK. (2006) *Bioorg. & Med. Chem. Let.,* **16***:*3287-3291.