

Final Scientific Report of the Short Term Scientific Mission STSM-5668

COST Action BM0806: Recent advances in histamine receptor H₄R research

Title: *Effect Of The H₄ Receptor Antagonist On The Cartilaginous, Vascular And Esophageal Histamine Content In Rats With Adjuvant Arthritis*

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Purpose of the visit was to investigate the effects of H₄ receptor antagonist JNJ7777120 on the histamine level of cartilage, peripheral blood vessels and oesophagus in normal rats and in a rat model of experimental arthritis. JNJ7777120 (10 and 30 mg/kg) was systemically administered to normal and adjuvant-challenged male Wistar rats 20 days before my visit. The first day of my STSM coincided with the day that the animals demonstrated arthritis signs with a maximum score of 16 based on a semi-quantitative arthritis scoring scale used [1]. All animals were sacrificed by decapitation. The tissues extracted were: cartilaginous tissue from the costosternal junction of the 9th and 10th ribs, peripheral blood vessels (abdominal aorta, and inferior vena cava-IVC) and the oesophagus. The tissues extracted from all animal groups were weighted and the net weight was recorded in ng before their storage at -20°C. In the following days we prepared all tissue samples for determination of their histamine content. Tissue histamine levels were quantified according to the Shore method with some minor modifications. Briefly, tissues were homogenized in 0,4N HClO₄ and then extracted in organic solvents (butanol and heptane). After the final step of the procedure histamine was extracted into 2N H₂SO₄ and *o*-phthalaldehyde was added. Histamine was measured fluorophotometrically with excitation wavelength of 360 nm and emission wavelength of 450 nm. Lower histamine levels were detected in the abdominal aorta than in the IVC. Administration of JNJ7777120 reduced IVC histamine levels in adjuvant-treated animals. These results provide evidence towards the H₄ receptor functionality in peripheral blood vessels. Interestingly, the JNJ7777120-induced reduction of histamine levels in blood vessels, contrary to the failure of the antagonist to exert a related action on cartilage in this animal model provides the lead for ongoing research on H₄ receptor systemic function. Furthermore, the effect of JNJ7777120 on the cartilaginous and oesophageal histamine levels could be attributed to an increase histamine anabolism and/or decrease histamine catabolism. Therefore we decided to continue the collaboration between host institute and my home institute. I am investigating the expression and the activity of two main histamine degrading enzymes diamine oxidase and histamine-N-methyltransferase in my home laboratory. Using the experimental model of arthritis I was shown during my STSM in the future I will measure the effect of the H₄ receptor antagonist, JNJ7777120, on the expression and activity of both histamine degrading enzymes in the same tissue samples of normal and adjuvant-challenged rats.

[1] Zampeli E, Thurmond RL, Tiligada E. Effect of the H₄R antagonist JNJ7777120 on the cartilage histamine content in rats with adjuvant arthritis. *Fund Clin Pharmacol* 2008;22:S10