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The role of the alpha 7 nicotinic acetylcholine receptor in inflammation and brain injury

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, Göteborg, fredagen den 4 februari 2022, klockan 13:00

av

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Docent Anja Meissner
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Avhandlingen baseras på följande delarbeten:

I. **Polymorphisms in alpha 7 nicotinic acetylcholine receptor gene, CHRNA7, and its partially duplicated gene, CHRFAM7A, associate with increased inflammatory response in human peripheral mononuclear cells.**
Pattanaik B*, **Hammarlund ME*,** Mjörnstedt F*, Ulleryd MA, Zhong W, Uhlén M, Gummesson A, Bergström G and Johansson ME
Submitted
**Equal contributions*

II. **The selective alpha7 nicotinic acetylcholine receptor agonist AR-R17779 does not affect ischemia–reperfusion brain injury in mice.**
Hammarlund ME, Darsalia V, Mjörnstedt F, Pattanaik B, Mallard C, Rocha-Ferreira E, Patrone C and Johansson ME
Bioscience Reports (2021) 41:6

III. **The role of the alpha 7 nicotinic acetylcholine receptor in neonatal brain injury**
Hammarlund ME, Akar S, Karlsson A, Pattanaik B, Mjörnstedt F, Svedin P, Ardalan M, Rocha-Ferreira E, Ek J, Mallard C and Johansson ME
Manuscript

SAHLGRENSKA AKADEMIN

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The role of the alpha 7 nicotinic acetylcholine receptor in inflammation and brain injury

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The alpha 7 nicotinic acetylcholine receptors (α7nAChR) are expressed in the nervous system as well as on peripheral immune cells where it participates in the cholinergic anti-inflammatory pathway. Inflammation is a common component in the pathology of many diseases and injuries, including brain damage. Stroke and neonatal encephalopathy are common causes of mortality and morbidity worldwide in adults and infants, respectively, but lack sufficient treatment strategies. This thesis aims to deepen the knowledge of α7nAChR involvement in immune regulation in human immune cells, and to investigate the treatment effect of α7nAChR stimulation in experimental models of adult and neonatal brain injury.

In **Paper I**, expression of the α7nAChR encoding gene *CHRNA7* and its partially duplicated gene *CHRFAM7A* were investigated in human peripheral blood mononuclear cells (PBMCs) from the healthy Swedish SciLifeLab SCAPIS Wellness Profiling (S3WP) cohort, and whether single nucleotide polymorphisms (SNPs) in these genes could affect clinical parameters as well as the immune response. Gene expression of *CHRNA7* and *CHRFAM7A* was positively correlated, and *CHRFAM7A* expression was four times higher than *CHRNA7* expression. Furthermore, one SNP, rs34007223, was associated with high sensitivity CRP (hsCRP) levels and nine SNPs in *CHRNA7* and/or *CHRFAM7A* were associated with altered PBMC cytokine response. In **Paper II**, the expression of *Chrna7* was investigated in different regions of the naïve adult mouse brain, and the treatment effect of the α7nAChR agonist AR-R17779 on stroke-induced injury was investigate using the middle cerebral artery occlusion (MCAO) model in mice. *Chrna7* was shown to be expressed in all investigated brain regions with the highest expression in hippocampus and cortex. Although a small effect on white blood cell count was observed, the agonist had no effect on injury outcome in the MCAO model. In **Paper III**, the effect of α7nAChR stimulation on neonatal encephalopathy was investigated using a mouse model of hypoxia-ischemia, and whether this effect might be sex dependent. No effect was observed on injury outcome seven days after insult. However, cytokines CCL2, CCL5 and IL-6 were shown to be decreased in the injured brain hemisphere 24 hours after insult in male, but not female, α7nAChR-stimulated mice.

The findings in this thesis support the role of both *CHRNA7* and *CHRFAM7A* as important regulators of the immune system in humans. Although α7nAChR stimulation had no effect on outcome in adult or neonatal brain injury models, minor effects on immune response were observed by the treatment. Notably, the immunomodulatory effect in the neonatal model was sex dependent and suggests that inclusion of both male and female subjects is of importance when evaluating α7nAChR function.

Keywords: alpha 7 nicotinic acetylcholine receptor, inflammation, brain injury, CHRNA7, CHRFAM7A, stroke, hypoxia ischemia, neonatal encephalopathy, human, PBMC

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