

MICROGLIAL GLUTAMATE TRANSPORTERS

Regulation of Expression and Possible Physiological Functions

AKDEMISK AVHANDLING

som för avläggande för medicine doktorexamen vid Göteborgs Universitet kommer att försvaras offentligt i föreläsningssal ”Inge Schiöler”, Medicinargatan 11, Göteborg

Tisdagen den 5:e juni 2007, kl 13.00

av

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Avhandlingen baseras på följande arbeten:

- I. Mikael Persson, Mona Brantefjord, Elisabeth Hansson, and Lars Rönnbäck. *Lipopolysaccharide increases microglial GLT-1 expression and glutamate uptake capacity in vitro by a mechanism dependent on TNF- α* . *GLIA* (2005) 2:111-120
- II. Jenny Jacobsson, Mikael Persson, Elisabeth Hansson, and Lars Rönnbäck. *Corticosterone inhibits expression of the microglial glutamate transporter GLT-1 in vitro*. *Neuroscience* (2006) 139:475-483
- III. Mikael Persson, Mats Sandberg, Elisabeth Hansson, and Lars Rönnbäck. *Microglial glutamate uptake is coupled to glutathione synthesis and glutamate release*. *European Journal of Neuroscience* (2006) 24:1063-1070
- IV. Mikael Persson, Marcela Pekna, Elisabeth Hansson, and Lars Rönnbäck. *The complement-derived anaphylatoxin C5a increases microglial GLT-1 expression and glutamate uptake in a TNF- α -independent manner*. Manuscript (2007)
- V. Mikael Persson, Mona Brantefjord, Jan-Åke Liljeqvist, Tomas Bergström, Elisabeth Hansson, and Lars Rönnbäck. *Microglial GLT-1 is up-regulated in response to herpes simplex virus infection to provide an antiviral defence via glutathione*. Manuscript (2007)

Handledare: Professor Lars Rönnbäck

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ABSTRACT

Microglia are considered as the immunocompetent cells of the central nervous system (CNS). Being the first line of defence, they have prominent roles in monitoring the homeostasis and the extracellular milieu and can rapidly and specifically react to any disturbances such as brain trauma, ischemia, neurodegenerative diseases, or infections. Microglia are normally adapted to a resting state, but due to alterations in the homeostasis they become activated. During pathological conditions it has been shown that microglia are able to express Na⁺-dependent high affinity glutamate transporters which are important for the uptake of the neurotransmitter glutamate. However, the mechanisms underlying the expression and the physiological role of it are not fully understood. In this thesis, it was found that the microglial glutamate transporter expression is connected to microglial activation and inflammatory events. The bacterial endotoxin lipopolysaccharide (LPS) was used to induce an environment mimicking neuroinflammation, a condition that occurs during almost any pathological condition in the CNS. It was found that LPS was able to increase the expression of the microglial glutamate transporter GLT-1 in a model system of essentially pure rat microglia. This effect was most likely mediated by the cytokine tumour necrosis factor- α (TNF- α), since the cytokine was able to mimic the effect of LPS by itself and the fact that antibodies against the TNF- α abolished the expression. Additionally, the LPS-induced increase in microglial GLT-1 expression could be inhibited by decreasing the release of TNF- α with the anti-inflammatory glucocorticoid corticosterone. The anaphylatoxin C5a, a component of the complement system, was also found to be able to induce microglial GLT-1 expression but in a different manner than LPS. The increased GLT-1 expression led to increased glutamate uptake from the extracellular space, which may be important to limit the excitotoxic effect of glutamate during pathological conditions. Furthermore, the increased glutamate uptake was directly coupled to an increased synthesis of the antioxidant glutathione. The glutamate partly fuelled the intracellular pool of glutamate in order to allow uptake of cystine, an amino acid that is one of the building blocks of the antioxidant glutathione, and was partly directly incorporated into glutathione. As a major antioxidant, glutathione was able to provide microglia with a self defence against reactive oxygen species. Furthermore, the increased glutathione levels provided microglia with better resistance to infections with herpes simplex virus due to the antiviral properties of the antioxidant. In response to herpes simplex virus infections, microglia are able to release TNF- α and up-regulate their GLT-1 expression in order to provide means for an increased glutathione synthesis and thus an increased viral resistance. In summary, the results show how microglial GLT-1 can be modulated and that increased resistance against oxidative stress and viral infections are two possible physiological functions of the increased microglial glutamate uptake.

Keywords: *anaphylatoxin, central nervous system, herpes simplex virus, glutamate transport, glutathione, GLT-1, lipopolysaccharide, microglia, neuroinflammation, oxidative stress, protection, tumour necrosis factor- α*