Effects of CyPPA on lipopolysaccharide-induced sickness responses, microglial activation as well as brain and systemic inflammatory mediators in mice

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N-cyclohexyl-N-[2-(3,5-dimethyl-pyrazol-1-yl)]-6-methyl-4-pyridinamine (CyPPA), a positive pharmacological activator of small conductance calcium-activated potassium channels, has been shown to antagonize lipopolysaccharide (LPS)-induced cytokine-expression in microglial cell cultures and, thus, has potential to treat neuroinflammation. Here, we aimed to investigate the effects of CyPPA on the brain during severe LPS-induced (2.5 mg/kg, intraperitoneal) systemic inflammation in mice. Pretreatment with CyPPA (15 mg/kg) injected 24 h prior and simultaneously with LPS-stimulation did not affect LPS-induced microglial activation, illness responses (depressed activity, anorexia and fever) and expression profiles of inflammatory mediators in the hypothalamus and in the periphery. However, CyPPA alone induced a rise in body core temperature that was accompanied by increased locomotor activity, decreased mRNA-expression of suppressor of cytokine signaling 3, increased expression of nuclear factor interleukin 6 and inhibitor of kappa B alpha in the hypothalamus while circulating cytokines were unaltered. Moreover, nuclear factor kappa B-activation was reduced in cortical neurons as revealed by western blot analyses potentially linked to some previously described neuroprotective capacities of CyPPA. Interestingly, we found reduced levels of adenosine, but a tendency of enhanced ATP and ADP in the liver of CyPPA-treated mice as measured by HPLC suggesting enhanced metabolism by CyPPA. Overall, while CyPPA might be suitable to modulate and treat some neuroinflammatory processes, the observed effects on metabolism, body core temperature and locomotor activity represent potential important side effects that should be taken into account.