Spontaneously hypertensive rats: a model of cerebrovascular neuro-inflammation?

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Spontaneously hypertensive rats (SHR) represent a model of hypertension and of vascular injury. In the past decade, SHR were also considered as a model of vascular dementia (VaD) and several studies have evidenced that the cerebrovascular changes in SHR may mimic brain vascular diseases of hypertensive individuals.

Vascular and cerebrovascular changes during hypertension are often linked to inflammatory processes. Inflammation frequently affects vascular endothelium, perivascular astrocytes and other glial cells forming the blood brain barrier (BBB). This inflammatory reaction may lead to neuro-inflammation with consequent damage of brain tissue.

In a recent work, SHR were studied as a model of early-stage cerebral small vessel disease. A significant brain atrophy and a reduction of white matter volumes, with areas of white matter demyelination and of circumscribed BBB dysfunction were found in SHR. Micro- and macrogliosis in deep cortical regions were also observed. Other studies have shown substantial disparities in cerebral CD45high leukocyte counts and distribution patterns between hypertensive and normotensive rats, with lower counts of T cells in the choroid plexus and meningeal spaces of SHR as well as decreased interleukin-10 levels in the cerebrospinal fluid. On the other hand, both T and NK cells were significantly increased in the SHR brain microvasculature.

Cholinergic precursors increasing choline availability and acetylcholine synthesis/release may represent a therapeutic approach for countering cognitive impairment occurring in adult-onset dementia disorders. Choline alphoscerate is among cholinergic precursors the most effective in enhancing acetylcholine biosynthesis and release in animal models.

Based on these findings, we have designed this study to confirm the inflammatory components of hypertension and to define neuro-inflammation entity in SHR, using appropriate methodological approaches and inflammation markers. These markers included endothelial adhesion molecules [intercellular adhesion molecules-1 (ICAM-1); platelet endothelial cell adhesion molecule-1 (PECAM-1) and vascular cell adhesion molecule-1 (VCAM-1)], pro-inflammatory interleukins (IL-1β, IL-6, TNFα and IL-18) and markers of BBB integrity (AQP4, S-100β, and Claudin-5). In these experiments choline alphoscerate (150mg/Kg/die) was used as a possible cerebrovascular protective and anti-inflammatory compound.

In the SHR cerebrovascular tree the expression of endothelial adhesion molecules was significantly increased in comparison to normotensive Wistar-Kyoto rats. Treatment with choline alphoscerate reduced the VCAM-1, PECAM-1, but not ICAM-1 immunoreactivity and countered changes of the pro-inflammatory interleukins expression. Moreover in SHR, BBB was impaired with an increase of immunoreactivity for AQP-4 and a decreased expression of Claudin-5 were. These BBB changes were partially countered by choline alphoscerate treatment. In SHR brain, an obvious glial reaction was found for both glial fibrillary acidic protein (GFAP)-immunoreactive astrocytes and for microglia. Glial reaction was countered by treatment with choline alphoscerate.

The above data suggest that SHR represent a reliable model of brain cerebrovascular damage and neuroinflammation related to hypertension. These findings have also shown that treatment with choline alphoscerate had a positive impact on different inflammatory markers investigated. This may bring to develop applications of the compound in the treatment of cerebrovascular disorders.