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Modulation of glial activation and amyloid burden by telmisartan: *In vitro* and *in vivo* studies

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The circulating renin-angiotensin system (RAS) is a fundamental regulatory mechanism of blood pressure conserved through evolution. Apart from periphery, an intrinsic RAS was also identified in the brain in which the bioactive hormone, angiotensin II, plays multiple roles. Angiotensin II (Ang II) is formed from angiotensin I by angiotensin converting enzyme (ACE). It acts mainly through angiotensin type 1 receptors (AT1Rs) and can influence brain inflammation expressed in Alzheimer's disease (AD) models. Although increased levels of brain AT1Rs, Ang II and ACE were reported in AD models, the role of RAS in brain inflammation remains unclear. Telmisartan, a well-known anti-hypertensive drug and an AT1R blocker, was suggested to serve as a potential treatment for brain inflammation and AD. The present study showed that intranasally given telmisartan (1 mg/kg/day) for 3.5 weeks to 2 month significantly reduced amyloid burden and microglial activation by up to 50% in the cortex of five familial AD (5XFAD) mice. Hippocampal amyloid plaques and microglial activation in 5XFAD were also reduced following 2 months treatment with telmisartan by approximately 50% and 25%, respectively. Short term effects of telmisartn *in vivo* were compared to those of perindopril (angiotensin converting enzyme inhibitor) which exhibited a similar inhibitory effect on the expression of these associated AD markers. *In vitro* studies including LPS-induced BV2 microglia cells treated with telmisartan resulted in a significant attenuation of inflammatory mediators' production including tumor necrosis factor-α (~50% reduction), interleukin 1-β (~30% reduction) and nitric oxide (~60% reduction). Telmisartan effect on NO production in LPS-induced BV2 cells was confirmed in primary neonatal rat microglial cells as well. In LPS-induced primary microglial cells telmisartan reduced the NO production levels by up to 70% and in mixed glial cells by 60%. Our data may envision potential intervention with the progression of glial activation and AD with both telmisartan and perindopril. Moreover, the non-invasive intranasal delivery may serve as an efficient alternative for systemic administration to modulate the brain RAS.

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Bipolar disorder susceptibility loci in Latino populations

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Recent genome-wide association studies (GWASs) have identified numerous putative genetic polymorphisms associated with bipolar disorder (BD) and/or schizophrenia (SC). We hypothesized that a portion of these polymorphisms would also be associated with BD in the Latino American population. To identify such regions, we tested previously identified genetic variants associated with BD and/or SC and ancestral haploblocks containing these single nucleotide polymorphisms (SNPs) in a sample of Latino subjects with BD. A total of 2254 Latino individuals were genotyped for 91 SNPs identified in previous BD and/or SC GWASs, along with selected SNPs in strong linkage disequilibrium with these markers. Family-based single marker and haplotype association testing was performed using the PBAT software package. Empirical P-values were derived from 10 000 permutations. Associations of eight a priori GWAS SNPs with BD were replicated with nominal ($P \leq .05$) levels of significance, including SNPs within nuclear factor I A (NFIA), serologically defined colon cancer antigen 8 (SDCCAG8), lysosomal associated membrane protein 3 (LAMP3), nuclear factor kappa B subunit 1 (NFKB1), major histocompatibility complex, class I, B (HLA-B) and 5′ -nucleotidase, cytosolic II (NT5C2) and SNPs within two intragenic regions. These results indicate that some of the gene variants found to be associated with BD or SC in other populations are also associated with BD risk in Latinos. Variants in six genes and two intragenic regions were associated with BD in our Latino sample and provide additional evidence for overlap in genetic risk between SC and BD.

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