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POSTER PRESENTATIONS

The role of transforming growth factor-β in hypertension-induced cerebrovascular remodeling

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Background

Hypertension (HT) promotes structural and functional changes in the cerebral microcirculation that can provoke irreversible cerebrovascular injury, leading to neuronal loss and brain atrophy,[1] cognitive impairment, vascular dementia,[2] and Alzheimer's disease.[3] Currently, the mechanisms and consequences of such remodeling are not fully understood. Transforming growth factor (TGF)β is a morphogen that regulates cellular differentiation, induces endothelial-to-mesenchymal transition (EndoMT), and works as a contractile-to-synthetic switch in vascular smooth muscle cells (VSMC) phenotype.[4] Plasma levels of TGFβ are increased in HT patients, and in spontaneously hypertensive rats (SHR) that exhibit vascular fibrosis.[5] Although coincidental, causal roles through which elevated TGFbβ may drive cerebrovascular remodeling in the HT brain are suspected, but unproven. We hypothesize that HT-induced TGFβ drives cerebrovascular remodeling, which decreases blood-brain barrier and impairs cerebrovascular autoregulation.

Methods

Brain cortices and penetrating cerebral microvessels (BMVs) were isolated from male and female SHR and Wistar-Kyoto rats (WKY, control), and subjected to western blotting and immunofluorescence labeling for endothelial cell (EC) and VSMC differentiation markers, TGFβ canonical pathway markers SMAD2, 3 and 4, as well as basement membrane protein expression, and glial fibrillary acidic protein (GFAP) as a marker of astrocyte inflammation. Additionally, TGFβ-treated rat retinal microvascular endothelial cells (RRMECs), and human brain microvascular endothelial cells (hCMEC/D3) ± the TGFβ inhibitor vactosertib, were also subjected to western blotting and immunofluorescence labeling to assess endothelial cell (EC) and VSMC differentiation markers, as well as basement membrane protein expression.

Results

TGFb was significantly increased in SHR BMVs. Moreover, GFAP levels were significantly increased in the SHR cortex. The EC junctional proteins platelet endothelial cell adhesion molecule-1 (PECAM-1) and vascular endothelial-cadherin (VE-cadherin), were significantly decreased in SHR. In contrast, CRBP-1, a marker for synthetic VSMC, and collagen IV and fibronectin levels significantly increased in SHR. Interestingly, female SHR rats had significantly increased levels of SMAD2/3, which was not evident in male SHRs, indicating a possible role for the non-canonical TGFβ pathway in male SHRs. Additionally, TGFβ significantly increased α-smooth muscle actin (α-SMA) and decreased VE-cadherin expression in RRMECs and D3 cells, consistent with EndoMT. TGFβ inhibition with vactosertib reversed these effects and significantly suppressed a-SMA, and maintained VE-Cadherin similar to control RRMECs and D3s.

Conclusions

We now have strong evidence for HT-induced cerebrovascular remodeling, where TGFβ mediates loss of both smooth muscle and endothelial differentiated phenotypes. The reversal of these effects using TGFβ blockers suggests that therapy to modulate TGFβ may represent a means to control HT-induced cerebrovascular remodeling.

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Received for publication: 26 September 2022.
Accepted for publication: 14 October 2022.

Veins and Lymphatics 2022; 11:10964
doi:10.4081/vl.2022.10964

References

1. Dahlöf B. Prevention of stroke in patients with hypertension. Am J Cardiol 2007;100:17J-24J.
2. Emdin CA, Rothwell PM, Salimi-Khorshidi G, et al. Blood Pressure and Risk of Vascular Dementia: Evidence From a Primary Care Registry and a Cohort Study of Transient Ischemic Attack and Stroke. Stroke 2016;47:1429-1435.
3. Kelley BJ, Petersen RC. Alzheimer's disease and mild cognitive impairment. Neurol Clin 2007;25:577-609.
4. Meng XM, Nikolic-Paterson DJ, Lan HY. TGF-β: the master regulator of fibrosis. Nat Rev Nephrol 2016;12:325-338.
5. Lijnen PJ, Petrov VV, Fagard RH. Association between transforming growth factor-beta and hypertension. Am J Hypertens 2003;16:604-611.