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Therapeutic potential of oxytocin receptor signaling in vascular dementia

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Abstract

Background: We recently demonstrated a *de novo* upregulation of the oxytocin receptor (OXTR) in astrocytes located in the peri-infarct regions of subjects who died with vascular dementia (multi-infarct subtype). OXTR activation has been linked to antioxidant, anti-inflammatory, and angiogenic signaling, suggesting that OXTR upregulation is a novel protective target for vascular dementia, mixed dementias, and perhaps even cerebrovascular accidents. To test this hypothesis, we modeled OXTR upregulation in a novel rat model of vascular dementia.

Method: Four month-old spontaneously hypertensive, stroke prone rats are being randomized to receive cortical injections of adeno-associated virus (AAV, serotype 6) bearing either OXTR or green fluorescent protein (GFP) cDNA under control of the astroglial-specific GFAP promoter, followed by randomization to receive cortical injections of the vasoconstrictor endothelin-1 (ET-1) or saline vehicle (n = 16/group, balanced for sex). Following behavioral testing, rats are being analyzed postmortem for infarction lesion size, cerebrovascular pathology, and several mechanistic indices including markers for cell death, inflammation, and oxidative stress.

Result: Preliminary results (n = 6-8/group) showed that rats receiving AAV-OXTR and ET-1 displayed a nonsignificant 40% reduction in mean latency time to target on the Barnes maze compared to rats receiving AAV-GFP and ET-1 ($p = 0.7$). Similarly, OXTR/ET-1-treated rats showed a 110% increase in the mean ratio of time spent exploring novel vs. familiar objects on the Novel Object Task compared to GFP/ET-1-treated rats ($p = 0.08$). Postmortem histological analysis revealed a nonsignificant 60% reduction in infarct size in OXTR/ET-1 compared to GFP/ET-1 rats ($p = 0.08$).

Conclusion: Preliminary data are trending to support the concept that astrocytic OXTR signaling may have a therapeutic benefit for dementia resulting from cerebrovascular accidents.