Theme: Pre-clinical Research and Mechanisms of Disease

A Multi-Target Therapeutic Approach for Alzheimer's Disease: The Potential of Irbesartan

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Abstract:
Renin-angiotensin system (RAS) drugs, commonly used for hypertension, have shown potential to slow cognitive decline, fostering interest in Alzheimer's disease (AD). Beyond amyloid plaques and tau tangles, AD pathology involves neuroinflammation, oxidative stress and apoptosis. Therefore, this study aimed to evaluate the neuroprotective effect of RAS drugs in in vitro and in vivo AD models and unveil whether the most promising compound could be repurposed as a multi-target candidate for AD. Four RAS drugs — losartan, valsartan, irbesartan and enalapril—were tested in N2a and N2a-APPswe neuronal cell lines. Irbesartan was the most promising and, hence, administered intranasally (40 mg/kg) for 10 days to APP/PS1 mice (4 months old). In vivo study assessed memory and learning capacities, anxiety and locomotion activity as well as biomarkers of glucose metabolism, insulin sensitivity, mitochondrial function, oxidative stress, blood-brain barrier (BBB) integrity, inflammation and neuronal survival. Irbesartan elevated p-AKT and HMOX1 levels in vitro ($p<0.01$), supporting its selection for in vivo testing. Intranasal irbesartan significantly improved memory (NORT preference index, $p<0.05$) and decreased insulin resistance ($p<0.001$). Dendritic spines density ($p<0.05$), and mitochondrial function (OXPHOS, $p<0.05$) were also improved. Markers of apoptosis, including p-JNK, FAS ($p<0.01$), BAX, p-c-jun ($p<0.05$) and Casp3 ($p<0.0001$) as well as oxidative stress markers MDA ($p<0.05$) and 4-HNE ($p<0.01$) were decreased with the treatment, while antioxidant Gpx1 ($p<0.05$) was enhanced. BBB integrity was restored, as indicated by lower fibrinogen permeability ($p<0.001$) and higher claudin-5 level in hippocampus ($p<0.05$). Finally, the inflammatory markers NLRP3, IL1β and IL6 were also reduced ($p<0.05$). Therefore, our results demonstrated that irbesartan modulates multiple AD-related pathways, suggesting its multi-target effect in AD prevention, and eventually its repurposing.

Keywords: Irbesartan, Alzheimer's, intranasal, multi-target, repurposing