Alpha1A-Adrenoceptors in Cognition

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Research Abstract

DESCRIPTION (provided by applicant): Our major objective is to generate tools and data to support the hypothesis that ?1A-adrenergic receptor (ARs) agonists may be useful in ameliorating the cognitive decline in Alzheimer’s Disease (AD). In light of current disappointing clinical trials using anti-amyloid ? antibodies, a pharmaceutical approach that can protect the brain and increase cognitive functions is urgently needed. ?-AR 1 subtypes (?1A, ?1B, ?1D) are

members of the G-protein-coupled receptor family of proteins that bind the endogenous neurotransmitter, norepinephrine. Signal transduction by ?-ARs is involved in neurotransmission, but their roles in the CNS are not well understood. Regulation by the ?1-AR subtypes (?1A, ?1B, ?1D) is complex; however most of the animal studies have shown that chronic ?1B-AR activity is neurodegenerative while the ?1A-AR is neuroprotective (reviewed in 1). Previous studies assessing the roles of ?1-ARs in cognition have been variable and controversial. Most of the studies were published in the 1990s before the cloning of the receptors, generation of mouse models and full characterization of existing ligands. Previous studies used an injection of mildly selective ?1-AR agonists or antagonists and analyzed for acute cognitive effects. The selectivity of the drugs can be questioned since the different ?1-AR subtypes can regulate opposite phenotypes in the brain (1). There are also documented cases that drugs may have different or even opposite effects on cognition depending upon whether treatment is acute or chronic (2-5). Chronic drug exposure can lead to adaptive changes in synaptic plasticity through neurogenesis (9-11) or gene regulation (12). Long-term memory formation requires coordinated regulation of gene expression (6- 8). In addition, GPCRs also generate novel signal transduction pathways when they become internalized through chronic stimulation (reviewed in 13). Our laboratory is in a unique position to address this controversy with the use of unique mouse models we generated for the ?1-ARs that systemically over express constitutively active mutants (CAMs) and are chronically activated even when an agonist is not present. These mice provide the most selectivity in ?1-AR subtype signaling. We propose to generate another novel mouse model that will determine the role of these receptors in learning and memory and to potentially reverse the cognitive decline in Alzheimer’s Disease (AD). We have preliminary data that activation of the ?1A-AR subtype can increase cognition and synaptic plasticity. We have published that our mouse model that chronically stimulates the ?1A-AR subtype is expressed in cognitive centers of the brain (14), increased adult neurogenesis (15), hippocampal synaptic plasticity and long-term potentiation (LTP) and cognition (16). Normal mice treated with the ?1A-AR selective agonist cirazoline for at least 2 Mo recapitulated neurogenesis (15) and cognitive enhancement (16), while ?1A-KO mice had impairments. Review of literature suggests that a deficit in LTP induction is associated with AD and there is increasing evidence that suggests that impaired LTP is an event occurring early in AD pathology. Current clinical trials focused on amyloid immunotherapies have been disappointing and cognitive efficacy is questionable (17-8) and current anti-dementia drugs only offer temporary relief. In order to provide tools to study the mechanism and to provide pre-clinical data, our specific aims are to determine if long-term versus short-term ?1A-AR agonist can improve cognitive functions and synaptic plasticity in AD mice. We will also generate a cross of our transgenic overexpressed CAM ?1A-AR mouse with the 3xTg AD mouse model to determine if selective ?1A-AR activation can decrease the rate of cognitive impairment.

Further information available at:

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