Pharmacology of Stimulus Memory and Habit Formation

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USA

Title of project or programme

Pharmacology of Stimulus Memory and Habit Formation

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NIH (NIA)

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34

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Basic Behavioral and Social Science... Behavioral and Social Science... Biotechnology... Brain Disorders... Dementia... Mental Health... Neurodegenerative... Neurosciences

Research Abstract
The memory impairment associated with Alzheimers disease has long been associated with a loss in acetylcholine function and pathophysiology of the entorhinal/perirhinal, or rhinal cortex. In

monkeys, lesions of this region as well as cholinergic deafferentation lead to severe memory deficits. We recently compared the effects of selective infusion of the (cholinergic receptor) m1 antagonist pirenzepine, and the m2 antagonist methoctramine directly into the rhinal cortex. Our findings suggest that m1 and m2 receptor subtypes in the perirhinal cortex have functionally dissociable roles, and that visual recognition memory is critically dependent on the m1 receptor subtype. To examine further the muscarinic modulation of visual mnemonic function in the rhinal cortex, we manipulated an m1-associated K+ channel whose actions could potentially enhance local network connections to support visual memory formation. We conducted local microinfusions of the selective Kv7 KCNQ channel blocker XE 991 in monkeys performing a visual recognition task and compared these scores to ones following local microinfusions of saline or pirenzepine. Monkeys were trained on a recognition memory task length that required stimulus memory for a period of 4 – 6 minutes while maintaining performance levels of 75-80%. Our preliminary results suggest, as before, infusions of pirenzepine resulted in a visual recognition memory deficit, in contrast, infusions of the m1-associated K+ channel blocker XE 991 resulted in a dose-dependent improvement in recognition accuracy. Our findings provide support for the crucial role of muscarinic m1 receptor-associated pathways in perirhinal cortex for the successful formation of new visual object memories. To examine more about the m1 muscarinic-dependent intracellular signaling pathways that underlie critical synaptic changes important for memory we have begun a proteomics approach to uncover the molecular signaling pathways activated during memory formation in a region-specific manner using two techniques: laser capture microdissection and reverse phase protein microarrays. Sections of snap-frozen perirhinal tissue from Rhesus monkeys were prepared and stained for Nissl substance. Tissue subregions of perirhinal cortex (Layers III and V/VI), as well as hippocampus (cell body layers of CA1, CA3, and dentate gyrus and their corresponding dendritic fields), were isolated using laser capture microdissection. Lysed tissue samples were then printed onto reverse phase protein arrays (RPPA). These arrays were probed with antibodies against phosphorylated, as well as total, proteins involved in muscarinic signaling, synaptic transmission, and neuronal activity. We are now in the process of applying this methodology to elucidate which critical proteins have been activated in specific laminae of the perirhinal cortex during visual memory formation. It is clear that cholinergic function plays a major role in cortical cognitive function. Groups of large cholinergic and GABAergic neurons in the basal forebrain are known to project widely throughout the cerebral cortical mantle. This input is thought to modulate cortical excitability locally, thus influencing brain functions as diverse as stimulus processing, motivation, and learning. We measured changes to spontaneous fMRI fluctuations after reversibly inactivating components of the basal forebrain, including the nucleus basalis of Meynert. Unilateral inactivation of the basal forebrain had a strong impact on spontaneous activity in the injected hemisphere. These data demonstrate that resting state functional connectivity is, at least in part, shaped by long-range, common input projections arising from the basal forebrain. In a second series of experiments we examined the nature of spontaneous brain activity at rest using both fMRI and electrophysiology measurements with reversible inactivation. Initially we measured neural activity at several cortical sites while resting monkeys were scanned. The fMRI fluctuations, the neural fluctuations, and their temporal coupling, varied over time and were particularly influenced by the animal’s apparent state of wakefulness. In a follow-up set of experiments, we unilaterally and reversibly inactivated the Nucleus Basalis of Meynert in the basal forebrain. Following inactivation, the level of spontaneous fMRI correlation in the injected hemisphere was consistently and significantly lower than in the uninjected hemisphere. Together, the results suggest that, in the resting brain, the shared spontaneous fMRI signals

that serve as the basis of functional connectivity, are closely linked in neural fluctuations, are shaped by input from the basal forebrain, and are strongly influenced by spontaneous and induced changes in behavioral arousal. Our results suggest that in addition to the important role of acetylcholine for recognition memory in the medial temporal lobe it plays a larger role in regulation of cortical activity. At this time we are in the process of completing the above mentioned projects and thus there are no new results to present.

Lay Summary
Further information available at:

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Investments > €500k

Member States:
United States of America

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Alzheimer's disease & other dementias

Years:
2016

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