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13. ABSTRACT (Maximum 200 words)
Stimulating muscarinic acetylcholine receptors results in activation of various signal transduction pathways. The goal of the research was to investigate the selectivity of coupling of the currently known 5 subtypes of muscarinic receptors to these different second messenger pathways. Results indicate that m1 m3 and m5 muscarinic receptors are coupled to enhanced phosphoinositide hydrolysis, while m2 and m4 receptors are coupled to a decrease in cyclic AMP formation. Results also demonstrate efficient coupling of m5 muscarinic receptors to generation of nitric oxide.

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"Coupling of Brain Muscarinic Receptors to Second Messengers"

Esam E. El-Fakahany, Ph.D.

STATEMENT OF THE PROBLEM STUDIED:

Muscarinic acetylcholine receptors play very important roles in relation to regulation of brain functions. Mammalian brain contains five different subtypes of muscarinic cholinergic receptors which respond to the neurotransmitter acetylcholine. The main goal of the research project was to investigate the selectivity of coupling of these receptor subtypes to various second messenger signaling mechanisms.

SUMMARY OF THE MOST IMPORTANT RESULTS:

The selectivity of coupling of different subtypes of muscarinic receptors to various second messenger signaling pathways was studied in mammalian cell lines which are individually transfected with the genes which encode for each of the five subtypes of muscarinic acetylcholine receptors. Activation of m1, m3 or m5 muscarinic receptors resulted in a significant enhancement of the hydrolysis of phosphoinositides. On the other hand, activation of m2 and m4 muscarinic receptors resulted in inhibition of cyclic AMP formation. Some muscarinic receptor agonists are able to discriminate among various subtypes of the receptor by showing functional selectivity. Our studies demonstrated the importance of equalizing the number of expressed receptors for studying such agonist selectivity.

We also studied the selectivity of coupling of various subtypes of muscarinic receptors to another very important second messenger signaling mechanism, namely the generation and release of nitric oxide. Nitric oxide plays important roles in learning and memory. It had also been shown to be involved in neurotoxicity. Our studies demonstrated that m5 muscarinic receptors which are efficiently coupled to enhanced generation of nitric oxide. These receptors are localized in basal ganglia. Their efficient coupling to generation of nitric oxide might be important for cholinergic enhancement of dopamine release.

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LIST OF PARTICIPATING SCIENTIFIC PERSONNEL:

Sheng Zu Zhu

No degrees granted while employed on the project.

REPORT OF INVENTIONS: None.