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Research Article

Metabolic Roles of the M_3 Muscarinic Acetylcholine Receptor Studied with M_3 Receptor Mutant Mice: A Review

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Abstract

The M_3 muscarinic acetylcholine (ACh) receptor (M_3 mAChR) is expressed in many central and peripheral tissues. It is a prototypic member of the superfamily of G protein-coupled receptors and preferentially activates G proteins of the G_q family. Recent studies involving the use of newly generated mAChR mutant mice have revealed that the M_3 mAChR plays a key role in regulating many important metabolic functions. Phenotypic analyses of mutant mice that either selectively lacked or overexpressed M_3 receptors in pancreatic β -cells indicated that β -cell M_3 mAChRs are essential for maintaining proper insulin release and glucose homeostasis. The experimental data also suggested that strategies aimed at enhancing signaling through

β -cell M_3 mAChRs might be beneficial for the treatment of type 2 diabetes. Recent studies with whole body M_3 mAChR knockout mice showed that the absence of M_3 receptors protected mice against various forms of experimentally or genetically induced obesity and obesity-associated metabolic deficits. Under all experimental conditions tested, M_3 receptor-deficient mice showed greatly ameliorated impairments in glucose homeostasis and insulin sensitivity, reduced food intake, and a significant elevation in basal and total energy expenditure, most likely due to increased central sympathetic outflow and increased rate of fatty acid oxidation. These findings are of potential interest for the development of novel therapeutic approaches for the treatment of obesity and associated metabolic disorders.

Key Words: :

Glucose homeostasis | Insulin | Knockout mice | Muscarinic receptor | Transgenic mice

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