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Article Addendum

The role of M3-muscarinic receptor signaling in insulin secretion

Kok Choi Kong & Andrew B. Tobin

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Abstract

Recently, M3-muscarinic receptor (M3R) has been identified as the bona fide receptor responsible for the cholinergic regulation of glucose-induced insulin release. The molecula. These include t mobilization and acti evidence for G protei 3R. These include p Src family kinas ment of regul se studies which w targeting such pat d insulin secretio

This articl

Insulin secretion by β cells of the islets of Langerhans in the pancreas is a process tightly regulated by glucose and other circulating nutrients. It is also modulated by many other factors, including hormones and neurotransmitters. One of the most prominent of these regulatory mechanisms is mediated by acetycholine (Ach) originating from the parasympathetic cholinergic input.[1,2] Although cholinergic regulation of insulin release has been known for many years, the mechanism of regulation and in particular the identity of the subtype of cholinergic receptor responsible for this regulation has only recently been established. There are five cholingeric muscarinic receptor subtypes (M_1–M_5) and the work of Gautam and colleagues using transgenic and gene knockout technology have determined that the M_3-muscarinic receptor (M3R) is the bona fide acetylcholine receptor that is responsible for enhancing glucose-dependent insulin release in β cells.[3]

Molecular Mechanisms for M_3R-Mediated Insulin Secretion

The mechanism by which M3R regulates insulin release was thought to be primarily via G-protein depending signaling to the calcium and PKC pathways. As a prototypical $G_{q/11}$-coupled receptor, activation of M3R induces the hydrolysis of membrane phospholipid phosphatidylinositol-4,5-biphosphate (PIP_2), catalyzed by phospholipase C (PLC). This generates two second messengers, inositol-1,4,5-trisphosphate (IP_3) and diacylgly res while DAG act portant role in M

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inhibiting the mitogen activated protein kinase p38δ activity, which has inhibitory effects on PKD1 in β cells.[5]

Other studies have, however, returned to the importance of calcium signaling. Healy and colleagues demonstrated that the expression level of IP_3-receptors in β cells is crucial for M3R-mediated insulin release.[6] Binding of the adaptor protein ankyrin-B to the IP_3-receptors in β cells stabilizes the receptors and thus enhances the calcium signal in the cells.[6] Pancreatic islets from heterozygous ankyrin-B mutant ($ankB^{+/-}$) mice exhibited a reduction in both basal and carbachol-stimulated intracellular calcium release,[6] suggesting that the IP_3-receptor is stabilized in the open state.

In addition, the sodium channel designated NALCN, which is short for sodium leak channel non-selective, has also been demonstrated to play a role in M3R-mediated insulin release.[7] This channel, formerly named Rb21 then VGCNL1, belongs to the four domain ion channel family. M3R has been shown to activate this channel in the model pancreatic β cell line, MIN-6, via the Src family of tyrosine kinases (SFKs).[7] In addition, one more piece of the jigsaw puzzle is the regulators of G-protein signaling protein, RGS4. Ruiz de Azua and colleagues have demonstrated that RGS4 negatively modulate M3R-mediated insulin secretion in β cells due to its selective inhibition of M3R signaling in β cells.[8]

Hence, there appears to be a number of possible in vivo mechanisms that act in concert to regulate the early and late phases of insulin secretion by M3R (Fig. 1).

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This proposal has only been put to vigorous investigation in recent years. After identifying M3R as the bona fide acetylcholine receptor that is responsible for enhancing glucose-dependent insulin release, Gautam and colleagues performed a series of studies which concluded with the generation of transgenic mice that express a constitutively active mutant of M3R specifically in pancreatic β cells in order to mimick the effects of a drug that chronically activates β cell M3Rs.[10] These mutant mice exhibited markedly improved glucose tolerance and increased serum insulin levels as well as resistance to diet-induced glucose intolerance and hyperglycemia.[10] These studies strongly supported the hypothesis that chronic, sustained activation of β cell M3Rs might produce beneficial effects to glucose homeostasis, and further established the therapeutic potential for M3R selective agonists for the treatment of type II diabetes. However, due to the multiple peripheral actions of M3Rs such as smooth muscle contraction and saliva secretion, the use of such agonists may be limited by their possible side effects.

Clinical Targeting of M3R Signaling in Insulin Secretion in Disease

The notion of targeting M3Rs in disorders where insulin secretion is de-regulated such as type II diabetes runs into the difficulty of developing ligands that are selective to the M3R subtype and that do not also interact with the other muscarinic receptor subtypes, namely M1, M2, M4 and M5. The problems associated with developing subtype selective ligands centre on the fact that the acetylcholine binding site on muscarinic receptor

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The therapeutic efficacy of carvedilol in the treatment of heart disease has been attributable to the fact that this ligand can direct signaling of the β-adrenoceptor to the arrestin-dependent pathways.[13] Similar biased ligands that direct signaling of the M3R via arrestin signaling would be expected to potentiate insulin release at β-islets in a manner that results in reduced side effects since G-protein-dependent calcium signaling would be minimized.

It is also possible to target the signaling proteins downstream of M3Rs. In particular, PKD1 and ankyrin-B are two potentially promising targets as evidenced by both in vitro and in vivo data. Though homozygous PKD1-knockout ($PKD1^{-/-}$) mice are embryonic lethal,[14] deletion of PKD1 in INS1 insulinoma cells completely abolished the insulin release induced by glucose and carbachol.[5] siRNA-knockdown of PKD1 in mouse islets also impaired the M3R-mediated augmentation of glucose-induced insulin secretion.[4] Carbachol augmentation of glucose-induced insulin secretion was significantly impaired in islets prepared from $ankB^{+/-}$ mice or in rat islets following siRNA-knockdown of ankyrin-B.[6] In addition, $ankB^{+/-}$ mice exhibited hyperglycemia after oral ingestion of glucose and the R1788W mutation of ankyrin-B impaired its function in islets and is associated with type II diabetes in Caucasians and Hispanics.[6] These studies demonstrate that targeting the signaling pathways downstream of the M3R can effectively modulate insulin release.

Concluding Remarks

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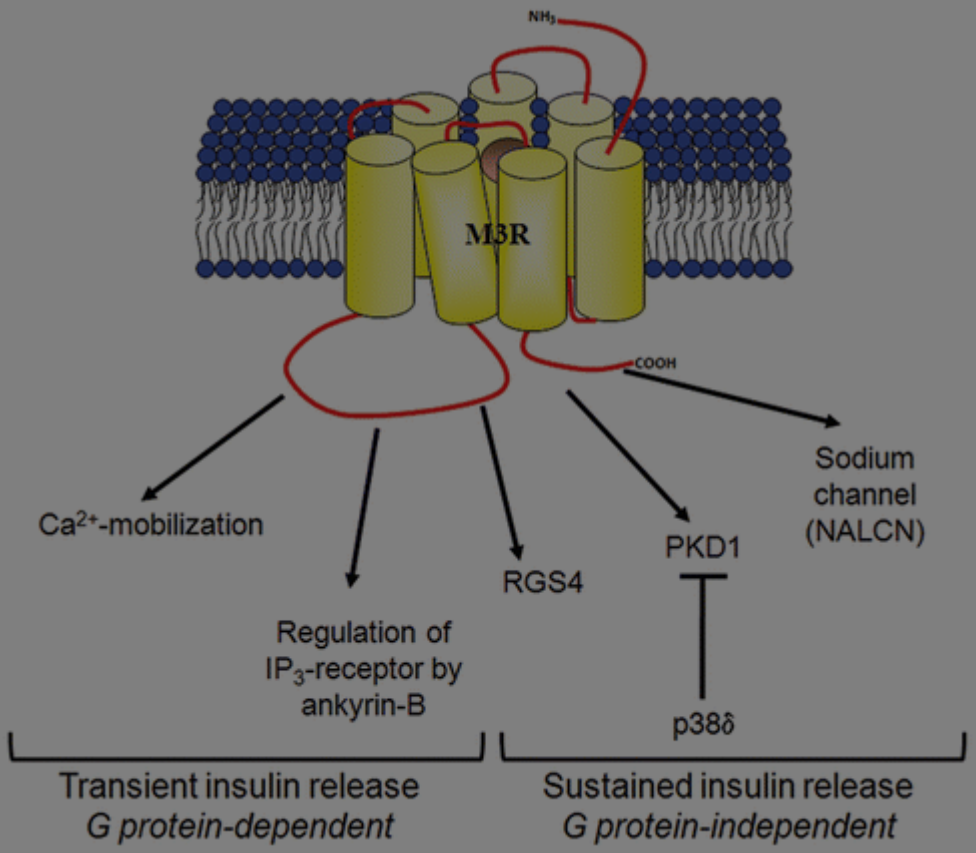
Figure

Figure 1 The possible mechanisms of M_3-muscarinic receptor (M3R)-mediated insulin secretion. Conventional studies have provided evidence that the transient, early phase of insulin secretion is mediated by M3R via G protein-dependent signaling that results in increase in intracellular calcium and activation of protein kinase C.[1] Recent studies have shown that the sustained, late phase of insulin secretion is enhanced by M3R via G protein-independent pathways which requires receptor phosphorylation/arrestin-dependent signaling to PKD1 [4] and Src family tyrosine kinases signaling to sodium channel NALCN.[7]



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Molecular Mechanisms for M R-Mediated Insulin Secretion
Physiological Implication of M3R-Mediated Insulin Secretion
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