Section: Miscellaneous

Review Article

RESEARCH PROGRESS IN MYOCARDIAL FUNCTION AND DISEASES RELATED TO MUSCARINIC ACETYLCHOLINE RECEPTOR

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ABSTRACT

Background: Muscarinic acetylcholine (ACh) receptors are widely distributed throughout the body and play an important role in cholinergic signal transmission. Among the five known muscarinic receptor subtypes, their specific roles in regulating myocardial function are still being explored. These receptors are involved in various cardiovascular conditions, including arrhythmia, myocardial ischemia, myocarditis, and myocardial fibrosis. This review highlights the current understanding of muscarinic ACh receptors in cardiac physiology and disease, with a focus on their signaling mechanisms and potential as therapeutic targets. This work was carried out at Bhima Bhoi Medical College and Hospital (BBMCH), Balangir, to contribute to ongoing research in cardiovascular pharmacology and myocardial protection.

Materials and Methods: A narrative review was conducted at **Bhima Bhoi Medical College and Hospital (BBMCH)** to evaluate the role of muscarinic acetylcholine receptors (mAChRs) in myocardial function, cardiovascular pathophysiology, and their therapeutic potential. Relevant evidence on receptor subtypes (M1–M5), signaling pathways, and cardiovascular diseases was reviewed.

Results: The M2 receptor is the predominant muscarinic receptor in the heart, with M1 and M3 receptors also contributing to cardiac regulation. Muscarinic receptors modulate heart rate, myocardial contractility, electrical conduction, calcium homeostasis, and cAMP-dependent signaling. Altered receptor activity is associated with myocardial infarction, arrhythmias, cardiac hypertrophy, fibrosis, myocarditis, and heart failure. These receptors influence myocardial injury, cardiac remodeling, and cardioprotective mechanisms.

Conclusion: Muscarinic acetylcholine receptors play a critical role in maintaining normal cardiac function and are involved in the development and progression of several cardiovascular diseases. Targeting muscarinic receptor signaling may provide novel therapeutic approaches for myocardial protection and the management of cardiovascular disorders.

Keywords: Muscarinic acetylcholine receptor, myocardial function, myocardial disease, myocardial toxicity, non-neuronal cholinergic system.

INTRODUCTION

Muscarinic acetylcholine receptors (mAChRs) are G protein-coupled receptors that play a crucial role in regulating cardiac function. Among the five receptor subtypes (M1–M5), the M2 receptor is predominantly expressed in the heart, while M1 and M3 receptors also contribute to cardiac physiological and pathological processes. These receptors influence heart rate, myocardial contraction, electrical conduction, and cardioprotective mechanisms. Alterations in muscarinic receptor signaling have been associated with various cardiovascular disorders, including myocardial infarction, cardiac hypertrophy, fibrosis, arrhythmias, and heart failure. Understanding the role

of muscarinic receptors in cardiac function may help identify novel therapeutic targets for the prevention and treatment of cardiovascular diseases.[1-3]

Muscarinic acetylcholine (ACh) receptors, particularly the M2 subtype, play an important role in regulating myocardial contraction by modulating heart rate, cardiac output, calcium homeostasis, and intracellular signaling pathways. Activation of these receptors generally reduces myocardial contractility, swhereas receptor inhibition can increase heart rate and contractile force. Muscarinic receptors also influence cardiac energy metabolism through cyclic adenosine monophosphate (cAMP)-dependent mechanisms and contribute to maintaining normal cardiac function. In myocardial infarction, muscarinic ACh receptors are involved in disease progression by regulating calcium channels and multiple signaling pathways that affect myocardial injury and cardiac remodeling. Alterations in muscarinic receptor activity may influence the severity and outcome of myocardial infarction, making them a potential therapeutic target in cardiovascular diseases.[4-6]

This review was undertaken in the Department of Pulmonary Medicine, Bhima Bhoi Medical College and Hospital (BBMCH), Balangir, with the objective of understanding the role of muscarinic acetylcholine receptors in cardiovascular pathophysiology and their potential clinical significance.

Table 1

Muscarinic receptor type	Target	Agonist/antagonist	CVDs	Publication year	(Refs.)
M2	Ca2+ channel	Ang-(1-7), ACh	Arrhythmia	2022	(9)
	Ca2+ channel	PAI	Arrhythmia	2019	(10)
	cAmp, IK	Atropine	Dilated cardiomyopathy, ischemic cardiomyopathy,	2011	(25)
			atrial tachyarrhythmias		
	Sympathetic	Yridostigmine,	Heart failure, hypertension	2024	(23)
	nerve	donepezil			
	RhoA, Racl,	Carbachol	Heart failure	2022	(13)
	RGS3L				
	Parasympathetic	Scopolamine,	Bradycardia	2020	(14)
	nerve	NMS, L-687306,			
		arecoline			
	Ca2+ ion channel	ACh	Atrial fibrillation	2022	(15)
	RyR2, PI3K	Carbachol	Heart failure	2020	(16)
	cAMP	Bile acid	Arrhythmias	2018	(12)
	cAMP	Carbachol, ACh	Cardiac arrest	2018	(26)
	CSPG4	Carbachol	Arrhythmia	2024	(27)
M3	L-type calcium	Tiotropium	Myocardial infarction	2019	(18)
	channel, CaMKII	bromide			
	Caspase-1, IL-1β	4-DAMP	Myocardial infarction,	2018	(29)
			heart failure		
M1, M2	Parasympathetic	Pirenzepine,	Bradycardia	1997	(28)
	nerve	atropine			
M2, M3	RyR2	AF-DX116,	Heart failure	2016	(17)
		J104129			
	Cyclo-	Carbachol	Heart failure	2014	(24)
	oxygenase-2				
M1, M2,	PKA-dependent	cAMP	Ischemia-reperfusion	2024	(19)
M3	phosphorylation,		injury		
	L-type calcium				
	channel				
	Vagal afferent	ACh	Heart failure	2020	(22)
	nerve				
	PDE4	Atropine	Tachycardia, arrhythmias	2017	(20)
	ANP secretion	Ursolic acid	Myocardial infarction	2014	(21)

ACh, acetylcholine; M, muscarinic ACh receptor; ACh, acetylcholine; cAMP, cyclic adenosine monophosphate; RGS3L, long isoform of the regu-lator of G protein signaling 3; CSPG4, chondroitin sulfate proteoglycan 4; RyR2, ryanodine receptor; PI3K, phosphoinositide 3-kinase; CaMKII, calcium ion/calcium-dependent protein kinase II; IL, interleukin; PDE4, phosphodiesterase 4; PKA, protein kinase A; RhoA, Ras homolog family member A; Rac1, Rac family small GTPase 1; ANP, atrial natriuretic peptide; PAI, phthalimide-azo-iperoxo; Ang-(1-7), angiotensin-(1-7); NMS, N-methylscopolamine; 4-DAMP, 4-diphenylacetoxy-N-methylpiperidine methiodide; L-687306, (3R,4R)-3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-1-azabicyclo[2.2.1]heptane; AF-DX116, 11-[[2-[(diethylamino)methyl]-1-piperidinyl]acetyl]-5,1 1-dihydro-6H-pyrido[2,3-b][1,4] benzodiazepin-6-one; J104129, (αR)-α-cyclopentyl-α-hydroxy-N-[1-(4-methyl-3-penten-1-yl)-4-piperidinyl]-benzeneacetamide fumarate.

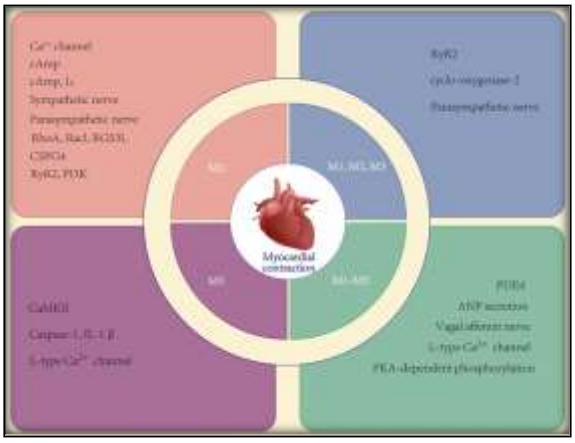

Figure 1: Regulatory effect of the muscarinic ACh receptor on myocardial contraction. The numerous cellular mechanisms include the activation of calcium and potassium channels, nerve and signal proteins, changes in biochemical indicators and changes in inflammatory factors, which may be involved in the contractile function of myocardium. M, muscarinic ACh receptor; ACh, acetylcholine; cAMP, cyclic adenosine monophosphate; RGS3L, long isoform of the regulator of G protein signaling 3; CSPG4, chondroitin sulfate proteoglycan 4; RyR2, ryanodine receptor; PI3K, phosphoinositide 3-kinase; CaMKII, calcium ion/calcium-dependent protein kinase II; IL, interleukin; PDE4, phosphodiesterase 4; PKA, protein kinase A.

Effects of muscarinic ACh receptors on myocardial ischemia and reperfusion injury

- I/R injury is strongly linked to muscarinic acetylcholine (ACh) receptors in the heart. Blocking these receptors (e.g., atropine, ipratropium, tiotropium) is associated with worsened myocardial I/R injury and toxicity.
- ACh is cardioprotective in I/R injury mainly by activating muscarinic receptors, which reduces infarct size and myocardial damage.
- Mechanisms of protection include:
  - ↓ Apoptosis of cardiomyocytes
  - ↓ Endoplasmic reticulum (ER) stress
  - Maintenance of mitochondrial function and autophagy balance
  - Regulation of Cx43 phosphorylation (Ser368)
- Preconditioning effect: Muscarinic receptor stimulation can trigger ACh-mediated ischemic preconditioning, protecting the heart from I/R damage.
- Key signaling pathways:
  - M3 receptor → CaMKβ → AMPK pathway → modulates mitochondrial function and energy metabolism
  - M2 receptor → ERK1/2 & PI3K/AKT pathways → promotes cell survival
- Drug-related findings:
  - Donepezil and other cholinergic agonists reduce apoptosis after I/R injury.
  - Catestatin–M2 receptor interaction supports cardioprotection via pro-survival signaling.

One-line takeaway: Muscarinic ACh receptor activation (especially M2 and M3) protects the heart from ischemia/reperfusion injury by reducing apoptosis, improving mitochondrial function, and activating survival signaling pathways [Figure 2].

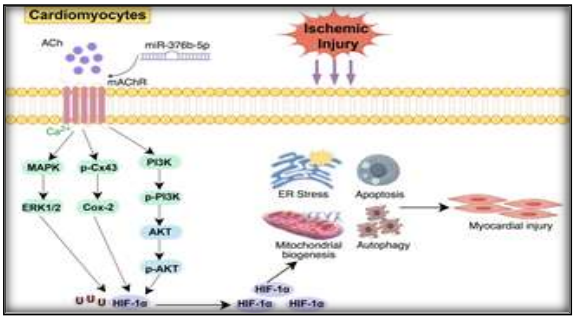

Figure 2: Regulatory mechanisms of muscarinic ACh receptor on myocardial infarction. ACh and miR-376b-5p can act on muscarinic receptors, affect HIF-1α through MAPK/ERK1/2, Cx43/Cox2 and PI3K/Akt, and affect cardiomyocyte apoptosis, autophagy, endoplasmic reticulum stress and mitochondrial biogenesis, and ultimately affect myocardial infarction. ACh, acetylcholine; M, muscarinic acetylcholine receptor; mAChR, muscarinic ACh receptor; MAPK, phospho-p38 mitogen-activated protein kinase; ERK1/2, extracellular signal-regulated kinase 1/2; Cx43, connexin 43; Cox-2, cyclooxygenase-2; PI3K, phos-phoinositide 3-kinase; Akt, protein kinase B; HIF-1α, hypoxia inducible factor-1α; ER, endoplasmic reticulum; miR, microRNA; p-AKT, phosphorylated AKT.

Effects of muscarinic ACh receptors on myocardial fibrosis: Myocardial fibrosis is common in cardiomyopathies, but its mechanisms are not fully understood. Cardiac fibroblasts play a central role, and muscarinic acetylcholine (ACh) receptors are increasingly recognized as important regulators.

Studies show that vagus nerve stimulation or activation of M3 muscarinic receptors can reduce myocardial fibrosis, potentially through the miR-29b/β-site APP-cleaving enzyme 1 pathway. In contrast, reduced ACh levels may promote fibroblast formation.

Clinically, elevated M2 muscarinic receptor autoantibodies are associated with more severe left atrial fibrosis and are higher in patients with atrial fibrosis compared to those without. Tissue studies also confirm a link between M2 receptors and fibrosis progression.

Additionally, M1 muscarinic receptors are upregulated in chronic atrial fibrillation and may influence the condition by regulating IK,ACh channels in atrial myocytes.

Overall, muscarinic ACh receptors (M1, M2, and M3) are closely involved in the development, diagnosis, and potential treatment of myocardial fibrosis.

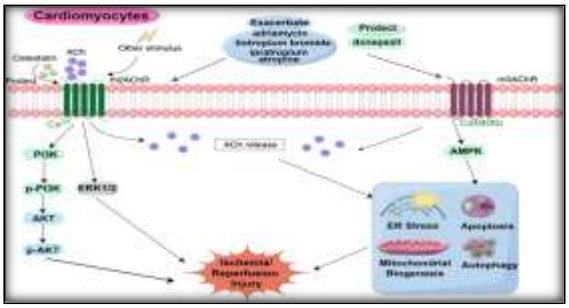

Figure 3: Role of muscarinic ACh receptor in myocardial ischemia and reperfusion injury. Ischemia/reperfusion injury may be regulated by drugs and stimuli through m2AChR receptors on PI3K/Akt and ERK1/2 pathways. Meanwhile, ischemia/reperfusion injury may be affected by ACh and drugs through m3AChR on cardiomyocyte apoptosis, autophagy, ER stress and mitochondrial biogenesis regulated by the AMPK pathway. ACh, acetylcholine; mAChR, muscarinic ACh receptor; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; p-AKT, phosphorylated AKT; ERK1/2, extracellular signal-regulated kinase 1/2; CaMKKb, calmodulin-dependent protein kinase kinase b; ER, endoplasmic reticulum.

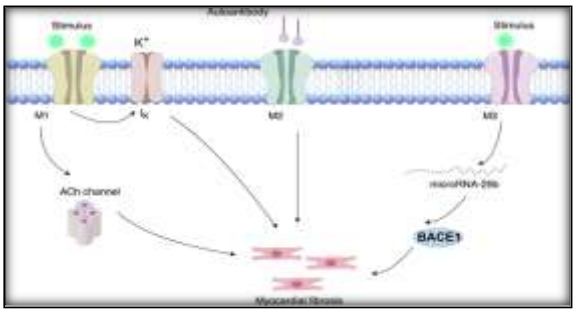

Figure 4: Mechanism of muscarinic ACh receptor in myocardial fibrosis. Stimulus and autoantibodies may affect myocardial fibrosis through ACh and potassium channels of M1, M2 and M3 receptor-mediated microRNA-29b/BACE1. M, muscarinic ACh receptor; ACh, acetylcholine; BACE1, beta-site app cleaving enzyme 1.

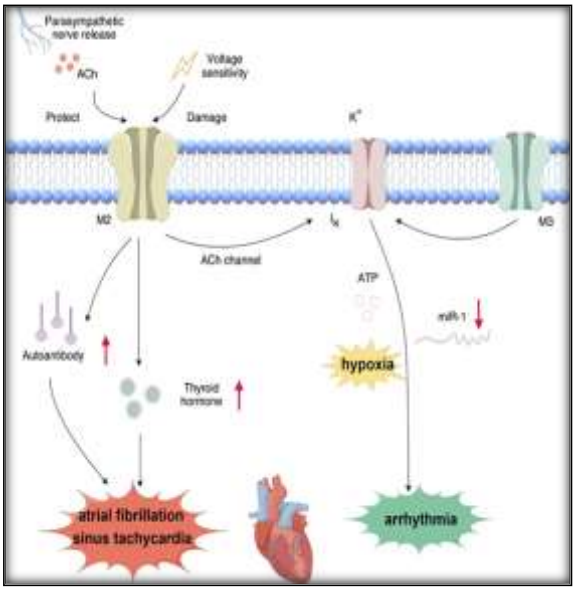

Figure 5: Effect of muscarinic ACh receptor on arrhythmia. ACh may protect against atrial fibrillation and sinus tachycardia caused by the increase of auto-antibodies and thyroid hormones through M2 receptors induced by voltage. Both M2 and M3 could regulate cardiomyocyte ATP, miR-1 and hypoxia through potassium ion channels to affect arrhythmia. M, muscarinic ACh receptor; ACh, acetylcholine; miR, microRNA.

Effects of muscarinic ACh receptors on arrhythmia

- Muscarinic acetylcholine (ACh) receptors play an important role in regulating heart rhythm and are closely linked to arrhythmias.
- Activation of these receptors can slow heart rate and may cause bradycardia.
- Blocking parasympathetic activity in the heart can promote ventricular arrhythmias and increase myocardial energy consumption.
- Muscarinic receptor agonists (including ACh) may help reduce arrhythmias, partly through regulation of IK-ATP potassium channels and protection during hypoxia.
- Atrial fibrillation (AF) is strongly associated with muscarinic receptor function:
  - Reduced ACh release after cardiac surgery can decrease AF occurrence.
  - M2 receptors may promote AF and sinus tachycardia by stimulating autoantibody and thyroid hormone release.
  - Patients with AF show elevated levels of M2 receptor autoantibodies.
  - Altered voltage sensitivity of M2 receptors has also been linked to AF and sinus tachycardia.
- M3 receptor overexpression appears protective, reducing arrhythmia incidence and mortality after ischemia-reperfusion injury by:
  - Decreasing arrhythmogenic miR-1 expression.
  - Increasing inward rectifier potassium current.
- Overall, muscarinic ACh receptors, particularly M2 and M3 subtypes, are promising targets for understanding and treating cardiac arrhythmias.

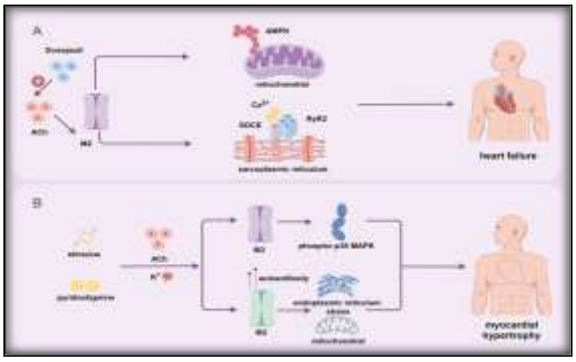

Figure 6: Effect of muscarinic ACh receptor on heart failure and myocardial hypertrophy. (A) Effect of muscarinic ACh receptor on heart failure. (B) Effect of muscarinic ACh receptor on myocardial hypertrophy. M, muscarinic ACh receptor; ACh, acetylcholine; AMPK, adenosine 5'-monophosphate-activated protein kinase; SOCE, store-operated calcium entry; RyR2, ryanodine receptor; MAPK, mitogen-activated protein kinase.

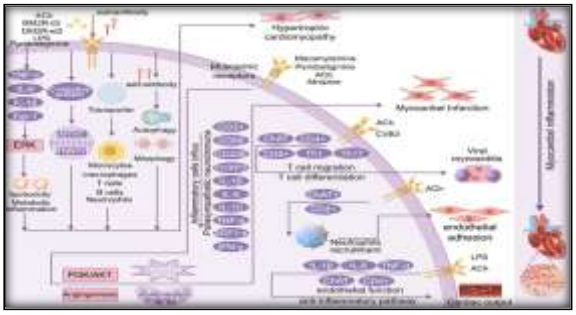

Figure 7: Role of muscarinic ACh receptor on myocardial inflammation. Drugs, chemicals and biological mediators may act on muscarinic ACh receptors to regulate various immune responses, affecting viral myocarditis, cardiac output and endothelial adhesion. The inflammatory responses could affect the regula-tion of myocardial injury through the ERK, PI3K/AKT, oxidative stress, mitochondrial function and angiogenesis pathways on the regulation of myocardial injury. M, muscarinic ACh receptor; ACh, acetylcholine; LPS, lipopolysaccharide; IL, interleukin; TNF, tumor necrosis factor; Egr-1, early growth response-1; ERK, extracellular signal-regulated kinase; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; CD, cluster of differentiation; FOXP3, forkhead box p3; SDF-1α, stromal cell-derived factor-lα; IFN-γ, interferon-γ; ChAT, acetylcholine transferase; Th, helper T cell; DM2R-el2, donor-immunized second extracel-lular loop of M2R; RM2R-il3, recipient third intracellular loop of M2R; MYH7, myosin heavy chain 7; TNNT2, troponin T2; CVB3, Coxsackievirus B3.

Effects of muscarinic ACh receptors on heart failure and myocardial hypertrophy

Heart Failure

- Activation of muscarinic ACh receptors, especially M2 receptors, has protective effects in heart failure.
- ACh improves calcium handling in cardiomyocytes through RyR2-mediated sarcoplasmic reticulum calcium release, helping reduce heart failure progression.
- Stimulation of M2 receptors limits ventricular remodeling and delays heart failure development.
- AChE inhibitors such as donepezil increase cardiac ACh levels and provide long-term cardioprotection.
- Increasing ACh through central or peripheral AChE inhibition improves autonomic balance, hemodynamics, and heart failure outcomes.
- ACh can reduce cardiomyocyte hypertrophy by activating muscarinic receptors and regulating AMPK-mediated mitochondrial remodeling.

Myocardial Hypertrophy

- Muscarinic ACh receptors, particularly M2 and M3, play important roles in regulating cardiac hypertrophy.
- Reduced M3 receptor–associated K^+ repolarization contributes to adverse cardiac remodeling, while M3 receptor overexpression is protective.
- Blocking M3 receptors may attenuate hypertrophy via inhibition of the p38 MAPK pathway.
- M2 receptors influence hypertrophy through effects on mitochondrial quality control and endoplasmic reticulum stress.
- Aerobic exercise improves hypertrophy partly through M2 receptor regulation.
- M2 receptor autoantibodies can induce myocardial hypertrophy.
- Pyridostigmine (an AChE inhibitor) reduces hypertrophy by prolonging ACh action at M2 receptors.
- However, excessive intermittent M2 receptor activation may worsen hypertrophy through oxidative stress.

Key takeaway: Moderate activation of muscarinic ACh receptors (especially M2 and M3) generally protects against heart failure and myocardial hypertrophy, although excessive M2 stimulation can have harmful effects.

Effects of muscarinic ACh receptors on myocardial inflammation

Table 2: Mechanisms of muscarinic ACh receptors in myocardial inflammation.

Function	Stimulus	Species	Target	Mechanism	Year	(Refs.)
Hypertrophic cardiomyopathy	M2 autoantibody	Homo sapiens	C-reactive protein, high-sensitivity C-reactive protein	MYH7 and TNNT2 genetic heterogeneity	2020	(91)
	RM2R-il3,	Mouse	Self-antibodies	Autophagy and	2018	(92)
	DM2R-el2			mitophagy		
	ACh, LPS	Mouse	Vesicular ACh	Monocytes/	2021	(103)
			transporter	macrophages,		

				T cells, B cells,		
				neutrophils		
	Pyridostigmine,	Mouse	TNF-α, IL-6,	Metabolic inflammation,	2018,	(100,101)
	ACh		IL-1β, ERK,	cardiac lipotoxicity	2023	
			Egr-1			
MI	Pyridostigmine	Rat	CD68, CD206,	Parasympathetic neuro-	2017	(93)
	bromide		FOXP3, IL-1β,	immune, oxidative		
			IL-6, IL-10,	stress		
			TNF-α			
	Pyridostigmine	Rat	IFN-γ, IL-6,	Mitochondrial	2019	(94)
	bromide		IL-1β, IL-10,	dysfunction,		
			TNF-α	inflammatory cell		
				influx, angiogenesis		
	ACh,	Rat	TNF-α, IL-6,	PI3K/AKT	2023	(99)
	mecamylamine,		IL-1β, CD31,			
	atropine		SDF-1α			
Viral	ACh	Mouse	ChAT, CD4+,	T-cell migration	2019	(96)
myocarditis			CD8+ T cells			
	CVB3	Mouse	CD4+ T cells,	CD4+ T-cell	2018	(98)
			Th1, Th17 cells	differentiation		
Endothelial	ACh	Mouse	CD4+ T-cells,	Recruitment of	2013	(97)
cell adhesion			ChAT+ B cells	neutrophils		
Cardiac	LPS	Rat	IL-1β, IL-6,	Cholinergic anti-	2018	(104)
output			TNF-α	inflammatory pathway		
	ACh	Homo sapiens	ChAT, CD4+	Vascular endothelial	2023	(105)
			T cells	function		

ChAT, choline acetyltransferase; ACh, acetylcholine; LPS, lipopolysaccharide; M, muscarinic ACh receptor; MI, myocardial infarction; ACh, acetylcholine; LPS, lipopolysaccharide; IL, interleukin; TNF, tumor necrosis factor; Egr-1, early growth response-1; ERK, extracellular signal-regulated kinase; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; CD, cluster of differentiation; FOXP3, forkhead box p3; SDF-1α, stromal cell-derived factor-lα; IFN-γ, interferon-γ; ChAT, acetylcholine transferase; Th, helper T cell; DM2R-el2, donor-immunized second extracellular loop of M2R; RM2R-il3, recipient third intracellular loop of M2R; MYH7, myosin heavy chain 7; TNNT2, troponin T2; CVB3, coxsackievirus B3.

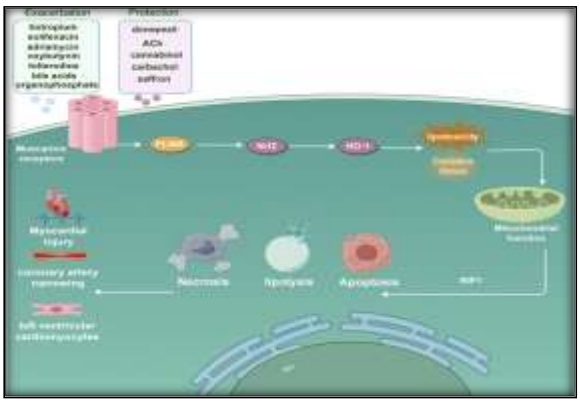

Figure 8: Muscarinic ACh receptors and regulation of cardiotoxicity. Numerous drugs and chemicals may act on muscarinic ACh receptors and affect the lipid toxicity and oxidative stress of cardiomyocytes through PLIN5, Nrf2 and HO-1. Subsequently, it affects cell apoptosis, necrosis and lipolysis by changing mitochondrial function and RIP1. These mechanisms ultimately affect the state of the coronary artery, myocardial cells and myocardial injury. ACh, acetylcholine; PLIN5, perilipin 5; Nrf2, nuclear factor erythroid 2-related factor 2; HO-1, heme-oxygenase-1; RIP1, receptor-interacting protein kinase 1.

Short Summary: Effects of Muscarinic ACh Receptors on Myocardial Inflammation

- Muscarinic acetylcholine (ACh) receptors help regulate myocardial inflammation through neural signaling and immune cell modulation.
- Increased M2 muscarinic receptor autoantibodies are associated with myocardial inflammation and cardiac dysfunction.
- Stimulation of cholinergic neurons produces anti-inflammatory effects and reduces inflammatory cytokines.
- Inhibition of acetylcholinesterase (AChE) increases ACh activity, helping prevent inflammatory autonomic dysfunction.
- Muscarinic receptors influence immune cells, especially T lymphocytes, contributing to anti-inflammatory responses.
- Infection increases choline acetyltransferase (ChAT) expression in $CD4^+$ and $CD8^+$ T cells, enhancing immune regulation.
- ACh and $ChAT^+$ B cells suppress macrophage activation.
- In viral myocarditis, ACh reduces inflammation by regulating $CD4^+$ T-cell differentiation and Th1/Th17 cytokines.
- Anti-inflammatory effects involve activation of the PI3K/AKT and ERK/Egr-1 signaling pathways, reducing inflammation and oxidative stress.
- $ChAT^+$ natural killer cells also provide immune-protective effects.
- Both muscarinic and nicotinic cholinergic receptors contribute to reducing cardiac inflammation.
- The non-neuronal cholinergic system may regulate inflammatory cells (e.g., macrophages and $FoxP3^+$ T cells), but its exact role in

myocardial inflammation remains uncertain and requires further research.

Key Point: Muscarinic ACh receptor activation generally exerts protective anti-inflammatory effects in the heart by modulating immune cells, cytokines, and intracellular signaling pathways.

Study on the muscarinic ACh receptors and cardiotoxic effects

Long-term use of anti-muscarinic drugs has been associated with cardiotoxicity, including worsening myocardial injury and increasing the risk of acute coronary syndrome. Drugs such as tiotropium, oxybutynin, solifenacin, and tolterodine have been linked to cardiovascular complications.

In contrast, activation of muscarinic ACh receptors, particularly the M2 subtype, appears to protect the heart. Studies show that receptor activation can reduce oxidative stress, apoptosis, and myocardial damage caused by adriamycin through pathways such as Nrf2/HO-1. Agents like donepezil and saffron have demonstrated cardioprotective effects by enhancing muscarinic receptor signaling. Increased acetylcholine release during parasympathetic stimulation also helps prevent cardiomyocyte death and reduces adriamycin-induced toxicity.

However, excessive stimulation of M2 receptors, such as by high bile acid concentrations or excessive cholinergic activation, may contribute to cardiotoxic effects, including coronary artery constriction and altered cardiac function.

Key point: Muscarinic ACh receptor inhibition is often associated with increased cardiac risk, whereas controlled receptor activation generally provides cardioprotection, although excessive activation may also be harmful.

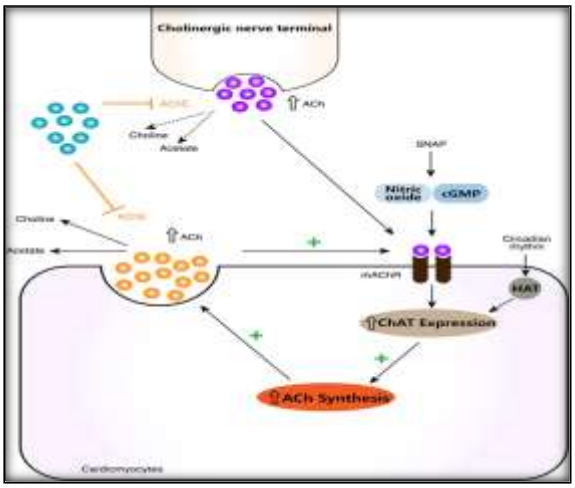

Figure 9: Mechanisms of muscarinic ACh receptors in the non-neuronal cholinergic system of cardiomyocytes. The cardioprotective mechanism of non-neuronal cholinergic system of cardiomyocytes is based on increasing the production of ACh. This includes stimulation of cholinergic neurons to electrically activate cholinergic neurons to produce and release ACh. Another possibility may be the pharmacological method of prolonging the effect of ACh by using AChE inhibitors. SNAP could activate muscarinic ACh receptor by transmitting nitric oxide and cGMP to cardiomyocytes, thereby increasing the synthesis and expression of ChAT and ACh. Finally, the circadian rhythm of the heart affects the synthesis and expression of ChAT and ACh by regulating HAT. mAChR, muscarinic ACh receptor; ACh, acetylcholine; AChE, acetylcholinesterase; SNAP, S-nitroso-N-acetyl-DL-penicillamine; cGMP, cyclic guanosine monophosphate; HAT, histone acetyltransferase; ChAT, ACh transferase.

The structure of left ventricular cardiomyocytes in rats, causing myocardial toxicity, while long-term treatment with cannabinol can significantly inhibit this toxic effect (116). A schematic illustrating the mechanisms of drugs acting on muscarinic ACh receptors with cardiotoxic effects is provided in [Figure 8].

Effects of muscarinic ACh receptors on the non-neuronal cholinergic system (NNCS): Muscarinic acetylcholine (ACh) receptors are key regulators of heart function and contribute to cardiac health by controlling calcium balance, mitochondrial activity, cell survival, autophagy, and inflammation. The myocardial non-neuronal cholinergic system (NNCS) highlights their therapeutic potential, making them promising targets for future cardioprotective treatments.

CONCLUSION

Muscarinic acetylcholine (ACh) receptors play a crucial role in regulating heart function and are closely associated with various cardiac diseases. They influence key processes such as calcium homeostasis, mitochondrial function, apoptosis, autophagy, and inflammation in cardiomyocytes. Although significant progress has been made in understanding their structure and function, their complete physiological and pathological mechanisms remain unclear. The emerging concept of the myocardial non-neuronal cholinergic system (NNCS) further highlights their importance and potential as therapeutic targets for developing future cardioprotective drugs.

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