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Letter to the Editor

M3 muscarinic acetylcholine receptor in cardiology and oncology

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Acetylcholine (ACh) [1–15] is an important neurotransmitter expressed in the central and peripheral nervous systems, in several non-neuronal cell types and also in most common cancer cells where it has been reported that the growth of tumor cells was accelerated via activation of muscarinic acetylcholine receptors (mAChRs) [16]. Nowadays the pathophysiological role of M_3 muscarinic acetylcholine receptor (M_3-mAChR) [16–18] remains still largely under observation [19]. M_3-mAChR plays an important role in cardiac function and heart disease [20–22] coupling to Gαq to activate the G_q-phospholipase C (PLC)-protein kinase C (PKC) pathway [23], and the delayed rectifying potassium current I_{KM3} [23,24] thus directly modulating cardiac membrane repolarization [25] and having anti-dysrhythmic (suppresses ischemic dysrhythmias) as well as pro-dysrhythmic (facilitates atrial fibrillation) actions [24]. M_3-mAChR distribution in cardiac tissue was found to be mostly confined to the intercalated disk region where it plays a role in ventricular gap junction-mediated cell-to-cell conduction [24] regulating the expression of phosphorylated connexin-43 (Cx43), a gap junction channel protein highly expressed in ventricular tissue and reduced in ischemia and Heart Failure(HF) [26] proposing these actions as protective against ischemia-induced arrhythmias [25,26].Research has suggested that M_3-mAChR activates anti-apoptotic signaling molecules, enhances endogenous antioxidant capacity, and diminishes intracellular Ca2 + overload, all of which contribute to protecting the heart against ischemic injuries [24,25]. It has been recognized that the M_3-mAChR promotes arrhythmias in atrial tissues (including playing a role in initiation and perpetuation of atrial fibrillation (27)) but suppresses ventricular arrhythmias. A role for RGS2, a putative regulator of the M_3-mAChR and for the selective M_3-mAChR antagonist darifenacin has been suggested in the management of AF [27] and the expression of M_3-mAChR appears to be increased in patients with atrial fibrillation [21,22,28,29], atrial dilatation [28], congestive heart failure [24,25], ventricular myocardial ischemia, and cardiac hypertrophy. It has been thought that the upregulation of M_3-mAChR plays an important role in modulating cardioprotection in hypertrophic heart [30,31] and in inhibing cardiac hypertrophy induced by angiotensin II (Ang II) [18]. It has also been thought that coronary artery spasm was related to the decrease of M_3-mAChR ′s density [32] and it has demonstrated both an endothelium-dependent relaxation to acetylcholine in coronary circulation mediated predominantly by the activation of M3-mAChR [33] and a M_3-mAChR mediated vasoconstriction in vascular smooth muscle cells in the absence of endothelium [19]. It has also demonstrated an endocardial endothelial M Rs mediate positive inotropy in response to muscarinic agonists via activation of COX-2 [34]. Further study is needed to evaluate differences in M_3-mAChR signaling caused by changes in receptor desensitization, sequestration [35–39], and up- or down-regulation and to elucidate the role of M_3-mAChR in cardiovascular system as well in inflammation and in cancer [39–83] while new findings are emerging as regards the use of cardiovascular drugs [38,55,68,69,74,75,77–79,82]. M_3-mAChR was involved in LPS-induced lung inflammation [84] and fibroblast proliferation [85] by mediating the NF-κB signaling pathway. Evidence suggests that the blockage of M_3-mAChR exerts anti-inflammatory properties [84]. It has been reported that M_3-mAChR is widely expressed in digestive tract cancer, and may play an important role in the proliferation, differentiation, transformation and carcinogenesis of tumors [86,87]. Muscarinic receptor agonists promote the growth of colorectal neoplasia [88] and findings suggest that vagal innervation contributes to gastric tumorigenesis via M_3-mAChR -mediated Wnt signaling [89] and mAChR activation, perhaps via M_1-mAChR and M_3-mAChR, induces lung epithelial cells to undergo epithelial–mesenchymal transition (EMT) proposed as a mechanism in the progression of airway

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diseases and cancer [90]. The antagonists of M_3-mAChR antagonist mAChRs have been demonstrated to depress the growth of small cell lung cancers (SCLCs) [16] and of non small cell lung cancers (NSCLCs). M_3-mAChR may also have a close relationship with prostatic oncogenesis [91]. Moreover a very interesting finding is the link of M_3-mAChR with epidermal growth factor receptor (EGFR)(75) and with Human ether-a-go-go-related gene K(+) channels (HERG)(69). EGFR is involved with PKC in mAChR -mediated activation of ERK1/2 in colon cancer cells [92] and mAChRs were identified as M_3-mAChR [93–95]. Muscarinic ligands with M_3-mAChR result in activation of ERBB1 with consequent stimulation of cell proliferation (95-96) Moreover Carbachol-mediated increase in hERG expression was abolished by the selective M_3-mAChR antagonist 4-DAMP (1,1-dimethyl-4-diphenylacetoxypiperidinium iodide). Carbachol reduced the hERG-ubiquitin interaction and slowed the rate of hERG degradation. Reseach has suggested that muscarinic activation increases hERG channel expression by phosphorylating E3 ubiquitin ligase Nedd4-2 via the protein kinase C (PKC) pathway [96,97]. Additional researches are needed to clearly elucidate the surprising role of M_3-mAChR and its journey could be longer than expected.

Conflict of interest

The author reports no relationships that could be construed as a conflict of interest.

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The author of this manuscript has certified that he adheres to the statement of ethical publishing as appears in International Journal of Cardiology.

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