LINK TO ORIGINAL ARTICLE

M_3 muscarinic receptors as targets for drug development in neurodegenerative disorders

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In their recent article, Wess *et al.*[1] (*Nature Rev. Drug Discov*. 6, 721–733; 2007) elegantly reviewed the power of mutant-mice studies to provide insights into the functions of muscarinic receptors for drug development purposes. These studies have highlighted the role of muscarinic receptor subtypes as targets for drug development in important conditions including diabetes, obesity, pain, asthma, Alzheimer's disease and schizophrenia, and should help to stimulate work in these areas. Other roles for muscarinic receptor signalling that were not covered in the Wess *et al.* review, but that may also be relevant to drug development, include the control of apoptosis in neural cells.

Yan *et al.*[2] demonstrated that activation of M_3 muscarinic receptors on cultured cerebellar granule cells inhibited apoptosis, and similar results have been reported using human neuroblastoma cell lines[3,4] and in M_3 muscarinic receptor transfected cells[4]. M_3 receptors are linked to several downstream pathways that may mediate this cell survival effect, including the anti-apoptotic gene *BCL2* (REF. 5), cyclic AMP response element binding protein (CREB)[6], hypoxia-inducible factor 1 (HIF1)[7], nuclear factor-κB (NF-κB)[8], and soluble amyloid precursor protein-α[8]. M_3 muscarinic receptor signalling may also mediate the cardioprotective effects of choline[9]. The coupling of the M_3 muscarinic receptor to the activation of CREB is especially relevant to cell survival given the important role of CREB in promoting survival of nerve cells[10].

These neuroprotective actions of M_3 muscarinic receptor activation may have implications for the treatment of nerve-cell death in neurodegenerative disorders such as Alzheimer's disease because M_3 receptors are widely expressed in the normal human brain and remain largely intact in Alzheimer's brain[11]. Furthermore, activation of the M_3 muscarinic receptor may aid in Alzheimer's disease by increasing the production of soluble amyloid precursor protein-α[12].

Although there is strong *in vitro* support for a cytoprotective role for M_3 receptor activation (as described above), the *in vivo* data in this area is sparse. Applying the power of the mutant-mouse technology, as described by Wess *et al.*[1] to this area of investigation would help determine whether these *in vitro* results are relevant to the *in vivo* situation and might translate to therapies for neurodegenerative disorders such as Alzheimer's disease.

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