Acetylcholine and Thyroid

Arterial Infusion of Acetylcholine and Thyroid Activity

SAM ROSE & PETER H. GLOW

Department of Physiology, University of Melbourne.
Department of Psychology, University of Adelaide.

ACETYLCHOLINE when added to incubated thyroid slices in vitro results in an increased rate of glucose catabolism and an increase in the proportion of glucose catabolized by the hexose monophosphate shunt pathway. Added thyroid stimulating hormone (TSH) has a similar effect\(^1\). This suggests that acetylcholine (ACh) may be able to mimic the action of TSH or that TSH acts by releasing ACh or an ACh-like substance to the target cells. The incubated in vitro slice technique does not allow investigation of the effects of ACh on the iodine metabolism or the morphology of the thyroid because these responses do not develop within the functional survival time of the in vitro slice. An acute intravenous injection of ACh will also cause a transient increased rate of iodine-131 release from the thyroid of the rabbit. The site of action of this ACh was not determined\(^2\).

References

Acetylcholine and Iodine Metabolism in Thyroid Slices.

1. George S. Serif

Summary

The action of acetylcholine on $^{131}$I metabolism in dog thyroid slices was investigated. It was established that acetylcholine, like the thyrotrophic hormone, increased the ability of thyroid slices to concentrate iodine. This augmented iodine uptake was found mainly in the form of increased amounts of protein bound monoiodotyrosine and diiodotyrosine.

References 3

were not, due to species variation, since acetylcholine only caused small increases in glucose oxidation of dog liver and pancreas.

Acetylcholine, at very low concentrations, increases the oxidation of glucose-1-C14 and glucose-6-C14 to O2 by thyroid slices. The concentration of acetylcholine needed is one that may exist in vivo in sympathetic ganglia (9). In addition, the magnitude, rapidity, and specificity of the effects observed argue for an important role of acetylcholine in thyroid physiology. Although the thyroid has profuse innervation, stimulation of its nerve fibers has failed to cause any consistent changes in thyroid physiology (10). However, most studies have been done with sympathetic stimulation, and acetylcholine is produced by parasympathetic fibers.

Note: Why is iodide used to make the salts for ACh-I and "muscarinic iodide" for research purposes – is it strictly for labeling (radio-iodide)? May be. Consider Pralidoxime Iodide used as therapeutic treatment though: why the iodide?

Acetylcholine iodide (CAS 2260-50-6)

CAS Number: 2260-50-6
Molecular Weight: 273.11
Molecular Formula: C7H16INO2

Refer to Certificate of Analysis for lot specific data (including water content).
**Ordering Information**

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Catalog #</th>
<th>Unit</th>
<th>Price</th>
<th>Qty</th>
<th>Add</th>
<th>Favorites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholine iodide</td>
<td>sc-257065</td>
<td>5 g</td>
<td>sc-257065</td>
<td>$200</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Description**

Acetylcholine iodide is an endogenous neurotransmitter at cholinergic synapses. Acetylcholine iodide amplifies the action potential of the sarcolemma thereby inducing muscle contractions.

The following description is from another company – I’m not clear if iodide is natural, or added as a label yet. I don’t get the feeling it’s natural, otherwise, there would be way more studies on it. I think the first description was in error?

**Application**

Acetylcholine is an endogenous neurotransmitter at cholinergic synapses that amplifies action potential of the sarcolemma thereby inducing muscle contractions. Acetylcholine iodide is used as an acetylcholine receptor agonist to identify, characterize and differentiate among types of cholinergic receptors. Acetylcholine iodide is used as a substrate to identify and characterize natural and mutated acetylcholinesterase(s).

**References**

J Clin Endocrinol Metab. 1980 Sep;51(3):500-2.

Presence and influence of cholinergic nerves in the human thyroid.

Van Sande J, Dumont JE, Melander A, Sundler F.

**Abstract**

There is evidence that the sympathetic nervous system exerts a control on human thyroid function via an adrenergic innervation of follicle cells. The present study demonstrates that cholinergic nerve fibers also reach follicle cells in the normal human thyroid. In addition, cholinergic agents were found to enhance cGMP accumulation in human thyroid tissue. This effect was blocked by atropine, a muscarinic receptor antagonist, but not by d-tubocurarine, a nicotinic receptor antagonist. These results provide morphological and biochemical arguments supporting a role of the parasympathetic nervous system in the regulation of thyroid function in man.
Presence and influence of cholinergic nerves in the mouse thyroid.

Melander A, Sundler F.

Abstract

The presence and influence of cholinergic nerves in the mouse thyroid was studied by histochemistry and measurements of changes in blood radioiodine (BRI) levels. Numerous nerve fibers displaying specific acetyl choline esterase activity were found, not only as a dense network around vessels but also as single fibers running around and between thyroid follicles. In stress-adapted normal mice, injection of carbamyl choline (CCh) reduced the BRI levels. In mice whose TSH secretion was suppressed by L-T4, neither CCh nor atropine had any measurable influence on the BRI levels when given alone. However, CCh pretreatment reduced and atropine pretreatment enhanced the TSH-induced BRI increase in such animals. It is concluded that the murine thyroid contains numerous cholinergic nerves that may influence not only thyroid blood flow but also thyroid hormone secretion directly. This direct influence appears to be an inhibitory one, mediated via muscarinic receptors in the follicle cells.


Cholinergic and VIPergic effects on thyroid hormone secretion in the mouse.

Ahrén B.

Abstract

The thyroid gland is known to harbor cholinergic and VIPergic nerves. In the present study, the influences of cholinergic stimulation by carbachol, cholinergic blockade by methylatropine and stimulation with various VIP sequences on basal, TSH-induced and VIP-induced thyroid hormone section were investigated in vivo in mice. The mice were pretreated with 125I and thyroxine; the subsequent release of 125I is an estimation of thyroid hormone secretion. It was found that basal radioiodine secretion was inhibited by both carbachol and methylatropine. Furthermore, TSH-induced radioiodine secretion was inhibited already by a low dose of carbachol. Moreover, a high dose of carbachol could inhibit VIP-induced radioiodine secretion. Methylatropine did not influence TSH- or VIP-stimulated radioiodine secretion, but counteracted the inhibitory action of carbachol on TSH- and VIP-induced radioiodine release. In addition, contrary to VIP, six various synthesized VIP fragments had no effect on basal or stimulated radioiodine release. It is concluded that basal thyroid hormone secretion is inhibited by both cholinergic activation and blockade. Furthermore, TSH-induced thyroid hormone secretion is more sensitive to inhibition with cholinergic stimulation than is VIP-induced thyroid hormone secretion. In addition, the VIP stimulation of thyroid hormone secretion seems to require the full VIP sequence.

Acetylcholine and norepinephrine: compared actions thyroid metabolism.

Maayan ML, Volpert EM, From A.

Abstract

Acetylcholine (ACh; 5 X 10(-4) M), like norepinephrine (NE; 6 X 10(-6) M), as shown previously, stimulated iodide organification by mouse thyroids in vitro, while at the same time it inhibited TSH- or (Bu)2cAMP-induced T4 release. However, thyroid cAMP was not changed by ACh, suggesting that ACh, like NE, exerted its effects at a step beyond cAMP production. Also, while ACh increased cGMP concentrations, (Bu)2cGMP and 8-bromo-cGMP were not effective on thyroid function in this system. Neurotransmitters, then, presumably do not exert their action through cyclic nucleotide stimulation ACh-induced stimulation of organification and inhibition of release was reversed by 10(-5) M atropine (ATR) but not by 10(-5) M d-tubocurarine, indicating that muscarinic receptors were involved. ATR also reversed inhibition of T4 release induced by NE, suggesting that the presynaptic cholinergic pathway may be responsible for stimulation of postsynaptic cholinergic and adrenergic neurotransmitters in the thyroid gland.

Muscarinic regulation of phospholipase A2 and iodide fluxes in FRTL-5 thyroid cells.

M Di Girolamo, D D'Arcangelo, C Bizzarri, D Corda

Laboratory of Cellular and Molecular Endocrinology, Istituto di Ricerche Farmacologiche Mario Negri, Consorzio Mario Negri Sud, S. Maria Imbaro, Italy.

Acta endocrinologica 09/1991; 125(2):192-200. DOI: 10.1530/acta.0.1250192

Source: PubMed

ABSTRACT FRTL-5 thyroid cells express a muscarinic receptor which inhibits the phospholipase C activity in a pirenzepine-insensitive manner. We here report that the cholinergic agonist carbachol decreases in these cells the steady-state iodide content, an effect correlated with the iodination of thyroglobulin and with thyroid hormone formation. Several signal pathways may be involved in this phenomenon since carbachol in addition to inhibiting phospholipase C, increased the arachidonic acid release and modified the adenyl cyclase activity. In FRTL-5 cells, arachidonic acid is released via the direct stimulation of phospholipase A2 by a pirenzepine-sensitive muscarinic receptor coupled to a GTP binding protein sensitive to pertussis toxin. Regarding adenyl cyclase, carbachol potentiated the thyrotropin-induced stimulation of the enzyme, whereas it did not affect the basal levels of cAMP. In vitro binding studies revealed the presence of two muscarinic binding sites. To summarize, the analysis of signal pathways and of in vitro binding sites indicates a complex muscarinic regulation of thyroid function, which includes the modulation of iodide fluxes.

References 3

[Characterization of muscarinic receptors in undifferentiated thyroid cells in Fisher rats].

Francisco Botella Romero, Elisa Martín Montañez, Eugenio Jiménez Gutiérrez, José Pavía Molina

ABSTRACT: The parasympathetic autonomous nervous system exerts control over thyroid function by activation of the muscarinic receptors in follicular cells. Various pharmacological and molecular subtypes of muscarinic receptors (M(1), M(2), M(3), M(4), M(5)) have been identified in central nervous system and peripheral tissues. Controversy surrounds receptor characterization in thyroid cells. Undifferentiated Fisher rat thyroid epithelial cells (FRT) were cultured. Association and dissociation kinetics assays and antagonist competition studies of the binding of (3)H-N-methylscopolamine ((3)H-NMS) to muscarinic receptors were performed to demonstrate the presence of muscarinic receptors. Specific muscarinic receptors in the plasma membrane of FRT cells were observed with an equilibrium dissociation constant (K(d)) of 0.44 nmol. The order of affinities obtained fitting the data to one binding site model in competition experiments with the muscarinic receptor antagonist was: dicyclomine > hexahydropilsidifenidol (HHSD) = 4-diphenylacetoxy-N-methylpiperidine methiodide (4-DAMP) > pirenzepine > himbaceine = 11-[[2-[(diethylamino)methyl]-1-piperidinyl]acetyl]-5,11-dihydro-6H-pyrido [4(14)]benzodiazepine (AF-DX 116). The results obtained indicate the existence of specific (3)H-NMS muscarinic binding sites located in the plasma membrane of FRT cells. The results obtained in competition experiments suggest that the receptors present in FRT cells belong to the M(3) subtype.


Summary of above abstracts:

This suggests that acetylcholine (ACh) may be able to mimic the action of TSH or that TSH acts by releasing ACh or an ACh-like substance to the target cells.

The magnitude, rapidity, and specificity of the effects observed [in this study] argue for an important role of acetylcholine in thyroid physiology.

These results provide morphological and biochemical arguments supporting a role of the parasympathetic nervous system [muscarinic receptors] in the regulation of thyroid function in man.

The parasympathetic autonomous nervous system exerts control over thyroid function by activation of the muscarinic receptors in follicular cells. The results obtained in competition experiments suggest that the receptors present in follicular cells belong to the M(3) subtype.

To summarize, the analysis of signal pathways and of in vitro binding sites indicates a complex muscarinic regulation of thyroid function, which includes the modulation of iodide fluxes.
Acetylcholine and Magnesium

Effects of magnesium ion on the interaction of atrial muscarinic acetylcholine receptors and GTP-binding regulatory proteins

Kazumasa Shiozaki, Tatsuya Haga

*Biochemistry, 1992, 31 (43), pp 10634–10642*

DOI: 10.1021/bi00158a028

Publication Date: November 1992

No access to the PDF, but here are a few lines:

“Furthermore, the data suggest that MgCl2 is not necessary for the formation of the mAChR-G-protein complex, but can induce a conformational change in the complex.”

“These results suggest that Mg is necessary for the action of mAChR on G-proteins, and that the agonist – mAChR—G protein complex formed in the presence of MgCl2 is an intermediate for the action of mAChr on G proteins.”

Magnesium reversal of lithium inhibition of β-adrenergic and muscarinic receptor coupling to G proteins

- Sofia Avissar,
- Dennis L. Murphy,
- Gabriel Schreiber

Abstract

Recently, lithium was found to inhibit the coupling of both muscarinic cholinergic and β-adrenergic receptors to pertussis toxin-sensitive and cholera toxin-sensitive G proteins respectively. These findings suggest that G proteins are the common site for both the antimanic and antidepressant therapeutic effects of lithium. Magnesium ions are crucial to the function of G proteins and interact with them at multiple sites. In the present study using rat cerebral cortex, we determined that magnesium can reverse the ability of lithium to inhibit isoprenaline- and carbamylcholine-induced increases in guanosine triphosphate (GTP) binding to G proteins. Lithium concentrations effective in attenuating G protein function were found to be hyperbolically dependent on free Mg2+ concentrations, suggesting multiple sites of competition between lithium and magnesium on G proteins. Free intracellular Mg2+ concentrations in rat cerebral cortex in vivo are known to be less than 1 mM. At such Mg2+ concentrations, therapeutically efficacious lithium concentrations (1 to 1.5 mM) were still able to alter G protein function, which supports the physiological and clinical relevance of lithium action on G proteins.
Corresponding author: Dr. Dennis L. Murphy, LCS, NIMH, NIH Clinical Center, 10-3D41, 9000 Rockville Pike, Bethesda, MD 20892.

From the book “Pediatric Critical Care Medicine: Basic Science And . . . . 2007, Derek S. Wheeler, Hector R. Wong, etc.

Magnesium:

- Acts at the level of the neuromuscular junction
- Decreases ACh release
- Diminishes the depolarizing action of ACh
- Depresses exciteability of smooth muscle membrane
- Necessary cofactor in Beta-Adrenergic signal transduction


Response of serum minerals (calcium, phosphate, and magnesium) and endocrine glands (calcitonin cells and parathyroid gland) of Wistar rat after chlorpyrifos administration. (Note: chlorpyrifos = AChE inhibitor. Also note: at least in abstract, Mg serum levels did not bounce back).

Tripathi S¹, Suzuki N, Srivastav AK.

Author information

¹Department of Zoology, DDU Gorakhpur University, Gorakhpur 273009, India.

Abstract

Wistar rats (male) were daily administered chlorpyrifos at a dose of 5 mg/kg b wt. and 10 mg/kg b wt. and sacrificed on 1st, 2nd, 4th, 6th, and 8th week. In chlorpyrifos exposed rats hypocalcemia, hypophosphatemia and hypomagnesemia were recorded. At later intervals an increased levels of serum calcium and phosphate were observed. The parathyroid glands and calcitonin cells exhibited increased activity which is evident by increased nuclear volume of these cells.


Effects of intravenous magnesium infusion on in vivo release of acetylcholine and catecholamine in rat adrenal medulla.

Komaki F¹, Akiyama T, Yamazaki T, Kitagawa H, Nosaka S, Shirai M.

References 3 website: JMR, http://fluoroquinolonetiyroid.com
Author information

- 1Department of Cardiac Physiology, National Cerebral and Cardiovascular Center Research Institute, 5-7-1 Fujishiro-dai, Suita, Osaka 565-8565 Japan; Department of Anesthesiology, Shiga University of Medical Science, Seta Tsukinowa-cho, Otsu, Shiga 520-2192, Japan.

Abstract

We applied microdialysis technique to the left adrenal medulla of anesthetized rats and examined the effects of intravenous Mg(2+) infusion on presynaptic acetylcholine (ACh) release and postsynaptic catecholamine release induced by electrical stimulation of splanchnic nerves. The dialysis probes were perfused with Ringer's solution containing neostigmine. Low-dose MgSO4 (25 μmol/kg/min for 30 min i.v.) increased mean plasma Mg(2+) concentration to 2.5mM; the administration suppressed norepinephrine (NE) release by approximately 30% and epinephrine (Epi) release by approximately 20%, but did not affect ACh release. High-dose MgSO4 (50 μmol/kg/min for 30 min i.v.) increased mean plasma Mg(2+) concentration to 3.8mM; the administration suppressed ACh release by approximately 25%, NE release by approximately 60% and Epi release by approximately 45%. Administration of Na2SO4 (50 μmol/kg/min for 30 min i.v.) did not change the release of ACh, NE or Epi. Local administration of nifedipine (200 μM) suppressed NE release by approximately 40% and Epi release by approximately 30%, but did not affect ACh release. In the presence of nifedipine, low-dose MgSO4 did not suppress the release of ACh, or further suppress NE or Epi compared to nifedipine alone, but high-dose MgSO4 suppressed ACh release by approximately 25% and further suppressed NE release by approximately 60% and Epi release by approximately 50% compared to nifedipine alone. In conclusion, intravenous administration of Mg(2+) inhibits both presynaptic ACh release and postsynaptic catecholamine release in the adrenal medulla, but L-type Ca(2+) channel-controlled catecholamine release may be more sensitive to Mg(2+) than non-L-type Ca(2+) channel-controlled ACh release.

Copyright © 2013 Elsevier B.V. All rights reserved.


Magnesium effect on the acetylcholinesterase inhibition mechanism: a molecular chromatographic approach.

Ibrahim F¹, Guillaume YC, Thomassin M, André C.

Author information

- 1Equipe des Sciences Séparatives, Biologiques et Pharmaceutiques (2SBP/EA-4267), Laboratoire de Chimie Analytique, Faculté de Médecine-Pharmacie, CHU-Jean Minjoz, Université de Franche-Comté, Place Saint Jacques, 25030 Besançon Cedex, France.

Abstract

The acetylcholinesterase enzyme (AChE) was immobilized on a chromatographic support to study the effect of magnesium on the binding mechanism of five AChE inhibitors (donepezil, tacrine, galanthamine, physostigmine and huperzine). The determination of the enthalpy and entropy changes of this binding at different magnesium concentration values suggested that van der Waals interactions and hydrogen bonds predominated the donepezil and tacrine association to AChE. As well, hydrophobic and electrostatic forces seemed to be the major interactions controlling the huperzine, galanthamine and
physostigmine association with AChE. In addition, it appeared that magnesium cation increased the binding affinity of galanthamine and physostigmine to the active site gorge of AChE. A comparison of the inhibitors hydrophobicity to their relative bound percentage with AChE showed an affinity enhanced with the increase in the molecule hydrophobicity and confirmed that the hydrophobic forces played an important role in the AChEI-AChE binding process. This novel biochromatographic column could be useful to find a specific inhibitor for this enzyme and so open new perspectives to be investigated.


Activation/deactivation of acetylcholinesterase by H2O2: more evidence for oxidative stress in vitiligo. (Copied this just to remind me of how prevalent ACh is –NOT just neuronal! In skin, and in tendons).

Schallreuter KU1, Elwary SM, Gibbons NC, Rokos H, Wood JM.

Author information

- 1Department of Biomedical Sciences, Clinical and Experimental Dermatology, University of Bradford, Bradford, West Yorkshire BD7 1DP, UK. K.Schallreuter@bradford.ac.uk

Abstract

Previously it has been demonstrated that the human epidermis synthesises and degrades acetylcholine and expresses both muscarinic and nicotinic receptors. These cholinergic systems have been implicated in the development of the epidermal calcium gradient and differentiation in normal healthy skin. In vitiligo severe oxidative stress occurs in the epidermis of these patients with accumulation of H2O2 in the 10(-3)M range together with a decrease in catalase expression/activity due to deactivation of the enzyme active site. It was also shown that the entire recycling of the essential cofactor (6R)-l-erythro-5,6,7,8-tetrahydrobiopterin via pterin-4a-carbinolamine dehydratase (PCD) and dihydropteridine reductase (DHPR) is affected by H2O2 oxidation of Trp/Met residues in the enzyme structure leading to deactivation of these proteins. Using fluorescence immunohistochemistry we now show that epidermal H2O2 in vitiligo patients yields also almost absent epidermal acetylcholinesterase (AchE). A kinetic analysis using pure recombinant human AchE revealed that low concentrations of H2O2 (10(-6)M) activate this enzyme by increasing the Vmax>2-fold, meanwhile high concentrations of H2O2 (10(-3)M) inhibit the enzyme with a significant decrease in Vmax. This result was confirmed by fluorescence excitation spectroscopy following the Trp fluorescence at lambdamax 280nm. Molecular modelling based on the established 3D structure of human AchE supported that H2O2-mediated oxidation of Trp(432), Trp(435), and Met(436) moves and disorients the active site His(440) of the enzyme, leading to deactivation of the protein. To our knowledge these results identified for the first time H2O2 regulation of AchE. Moreover, it was shown that H2O2-mediated oxidation of AchE contributes significantly to the well-established oxidative stress in vitiligo.


Sensitivity of acetylcholinesterase molecular forms to inhibition by high MgCl2 concentration.

Inestrosa NC1, Pérez CA, Simpfendorfer RW.

Author information
Abstract

Previous studies have shown that the asymmetric (A12) and the dimeric (G2), but not the tetrameric (G4), acetylcholinesterase (AChE) forms are inactivated by high MgCl2 concentration (Perelman and Inestrosa 1989 Anal. Biochem. 180, 227-230). Here we show that the effect of MgCl2 on AChE activity corresponds to an irreversible inhibition and is not due to environmental effects related to the different extraction media. The anchor domain in each AChE form was not involved in the differential MgCl2 sensitivity. Monomers derived from the various AChE forms behave in a way similar to that of the original assembled forms. Purified AChE molecular forms showed the same sensitivity to MgCl2, than the same enzyme forms studied in tissue extracts. Neither the affinity for the substrate nor the inhibition by excess substrate of the residual AChE activity were affected by high MgCl2 concentration. Results indicate that the differences between the tetrameric enzyme and the other two AChE molecular forms occur at the level of the catalytic subunit, probably due to differential post-translational processing.


Benefits of magnesium sulfate in the management of acute human poisoning by organophosphorus insecticides.

Pajoumand A¹, Shadnia S, Rezaie A, Abdi M, Abdollahi M.

Author information

¹Poison Control Center, Loghman-Hakim Hospital, School of Medicine, Shaheed-Beheshti University of Medical Sciences, Tehran, Iran.

Abstract

Organophosphorus chemicals (OPs) are the pesticides most often involved in serious human poisoning. Treatment of intoxication with OPs conventionally involves atropine for reduction of muscarinic signs and oximes that increase the rate of hydrolysis of the phosphorylated enzyme acetylcholinesterase (AChE). Although atropine and oximes (pralidoxime or obidoxime) are traditionally used in the management of such poisoning, their efficacy remains a major issue of debate; thus, the goal of this prospective clinical trial was to elaborate the value of magnesium sulfate (MgSO4) in the management and outcome of OP insecticide poisoning. This unicenter, randomized, single-blind trial study was conducted on patients who were acutely poisoned with OPs and admitted to the Poisoning Center of Loghman-Hakim Hospital in Tehran, Iran. In a systematic sampling, every fourth eligible patient was chosen to undergo MgSO4 treatment. Magnesium sulfate was administered at dose of 4 g/day i.v. continued for only the first 24 hours after admission. The mean daily oxime requirement and the mean daily atropine requirement were not statistically significant between two treated groups. The mortality rate and hospitalization days of patients who received MgSO4 treatment were significantly lower than those who had not received MgSO4 (P < 0.01). It is concluded that administration of MgSO4, in a dose of 4 g/day concurrent to conventional therapy, in OP acute human poisoning is beneficial by reducing the hospitalization days and rate of mortality.
Anticholinergic Side Effects

Look for similarities with FQ Toxicity

Look up Atropine and Toxidrome in Wikipedia

Look up side effects of pilocarpine (Salagen)

Look up evoxac- tendon issues only listed in SJS patients

atropine-inhibitable muscarinic receptors

gustatory rhinitis

vasomotor rhinitis

Gustatory Rhinorrhea

Atrovent: It is an anticholinergic bronchodilator chemically related to atropine. Other less serious side effects are more likely to occur, such as:

headache, dizziness;

dry mouth, cough, hoarseness;

nausea, upset stomach; or

blurred vision

This drug may make you dizzy or cause blurred vision or other vision changes. Do not drive, use machinery, or do any activity that requires alertness or clear vision until you are sure you can perform such activities safely. Limit alcoholic beverages. As an anticholinergic drug, cases of precipitation or worsening of narrow-angle glaucoma, glaucoma, halo vision, conjunctival hyperaemia, corneal edema, mydriasis, acute eye pain, dry throat, hypotension, palpitations, urinary retention, tachycardia, constipation, bronchospasm, including paradoxical bronchospasm have been reported with the use of ATROVENT. Additional adverse reactions identified for ATROVENT seen in clinical trials include throat irritation, stomatitis, mouth edema, and vision blurred.

Post-Marketing Experience

References 3  website: JMR,  http://fluoroquinolonethyroid.com
In a 5-year placebo-controlled trial, hospitalizations for supraventricular tachycardia and/or atrial fibrillation occurred with an incidence rate of 0.5% in COPD patients receiving ATROVENT CFC. Additionally, urinary retention, mydriasis, gastrointestinal distress (diarrhea, nausea, vomiting), cough and bronchospasm, including paradoxical bronchospasm, hypersensitivity reactions, intraocular pressure increased, accommodation disorder, heart rate increased, pharyngeal edema, and gastrointestinal motility disorders have been reported during the post-marketing period with use of ATROVENT.

Ocular Effects

ATROVENT HFA is an anticholinergic and its use may increase intraocular pressure. This may result in precipitation or worsening of narrow-angle glaucoma. Therefore, ATROVENT HFA should be used with caution in patients with narrow-angle glaucoma.

Patients should avoid spraying ATROVENT HFA into their eyes. If a patient sprays ATROVENT HFA into their eyes, they may cause eye pain or discomfort, temporary blurring of vision, mydriasis, visual halos or colored images in association with conjunctival and corneal congestion. Advise patients to consult their physician immediately if any of these symptoms develop while using ATROVENT HFA Inhalation Aerosol.

Inform patients that ATROVENT HFA may cause urinary retention and should be advised to consult their physicians if they experience difficulty with urination.

Mechanism of Action

Ipratropium bromide is an anticholinergic (parasympatholytic) agent which, based on animal studies, appears to inhibit vagally-mediated reflexes by antagonizing the action of acetylcholine, the transmitter agent released at the neuromuscular junctions in the lung. Anticholinergics prevent the increases in intracellular concentration of Ca++ which is caused by interaction of acetylcholine with the muscarinic receptors on bronchial smooth muscle.

SIDE EFFECTS: See also How to Use section.

Dizziness, nausea, stomach upset, or dry mouth may occur. If any of these effects persist or worsen, tell your doctor or pharmacist promptly.

Remember that your doctor has prescribed this medication because he or she has judged that the benefit to you is greater than the risk of side effects. Many people using this medication do not have serious side effects.
Infrequently, this medication may cause severe sudden worsening of breathing problems right after use. If you have sudden worsening of breathing, use your quick-relief inhaler and get medical help right away.

Tell your doctor right away if you have any serious side effects, including: vision changes, eye pain, fast/pounding heartbeat, difficult/painful urination.

A very serious allergic reaction to this product is rare. However, get medical help right away if you notice any symptoms of a serious allergic reaction, including: rash, itching/swelling (especially of the face/tongue/throat), severe dizziness, trouble breathing.

This is not a complete list of possible side effects. If you notice other effects not listed above, contact your doctor or pharmacist.

Links: Ach and NMDAR’s, Tenocytes, Bladder, Non-Neuronal, ColQ, MuSK, SJS, Muscarinic, Ganglionic, Lemon Balm, CNS symptoms, Thyroid, Mitochondria, Epitopes, Cholinesterase, Ocular

http://www.jneurosci.org/content/21/17/6949.long Acetylcholine Mediates the Estrogen-Induced Increase in NMDA Receptor Binding in CA1 of the Hippocampus and the Associated Improvement in Working Memory

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3582816/ Human tenocytes are stimulated to proliferate by acetylcholine through an EGFR signalling pathway

http://www.ics.org/Abstracts/Publish/44/000262.pdf MECHANISMS FOR STRETCH-INDUCED NON-NEURONAL ATP AND ACEHYLCHOLINE RELEASES FROM HUMAN BLDDER

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2518461/ Acetylcholine beyond neurons: the non-neuronal cholinergic system in humans (Good paper)

http://www.jbc.org/content/278/26/23233.long Two Different Heparin-binding Domains in the Triple-helical Domain of ColQ, the Collagen Tail Subunit of Synaptic Acetylcholinesterase

References 3  
C-terminal and heparin-binding domains of collagenic tail subunit are both essential for anchoring acetylcholinesterase at the synapse.

Genetic analysis of collagen Q: roles in acetylcholinesterase and butyrylcholinesterase assembly and in synaptic structure and function.

MuSK is required for anchoring acetylcholinesterase at the neuromuscular junction.

Antimuscarinic Antibodies in Sjogren’s Syndrome: Where Are We, and Where Are We Going? (Antibody tests for muscarinic)

Antidepressants inhibit human acetylcholinesterase and butyrylcholinesterase activity “At this moment, the exact physiological function of BuChE is not yet clear, but it is well known that this enzyme hydrolyses a variety of xenobiotics such as aspirin, succinylcholine, heroin and cocaine. . . The clinical antidepressants, fluoxetine, sertraline and amitriptyline are used worldwide. . . there are many indirect and undesirable effects presented in the therapy. Trycyclic antidepressants, like amitriptyline, are characterized by a high potential of anticholinergic side effects including memory impairments, delirium, behavioural toxicity and cardiovascular dysfunctions” (quote from actual paper).

Advances in toxicology and medical treatment of chemical warfare nerve agents (consider FQ tox as a nerve gas tox)

Cholinergic connectivity: it's implications for psychiatric disorders. “This review looks at the cholinergic system and its interactions with the intrinsic neurotransmitters glutamate and gamma-amino butyric acid as well as those with the projection neurotransmitters most implicated in the pathophysiologies of psychiatric disorders; dopamine and serotonin. In addition, with the recent focus on the role of factors normally associated with inflammation in the pathophysiologies of psychiatric disorders, links between the cholinergic system and these factors will also be examined”.

Muscarinic Adrenal Responses To Acetylcholine In Conscious Calves. “adrenal medullary and cortical responses to intraaortic infusions of acetylcholine at a low dose are mediated mainly by muscarinic receptors, as it has previously been shown that they are substantially reduced in the presence of atropine.”

Idiopathic Autonomic Neuropathy Comparison of Cases Seropositive and Seronegative for Ganglionic Acetylcholine Receptor Antibody

Anti-stress effects of lemon balm-containing foods
Modulation of mood and cognitive performance following acute administration of single doses of Melissa officinalis (Lemon balm) with human CNS nicotinic and muscarinic receptor-binding properties

http://www.myasthenia.org/LinkClick.aspx?fileticket=JuFvZPPq2vg%3D Medications and Myasthenia Gravis (A Reference for Health Care Professionals) “Magnesium interferes with neuromuscular transmission by inhibiting release of ACh. Magnesium competitively blocks calcium entry at the motor nerve terminal. There may also be a milder postsynaptic affect. Clinically, hypermagnesemia resembles Lambert-Eaton syndrome more so than autoimmune MG. In addition, magnesium can potentiate the action of neuromuscular blocking agents, which has been emphasized in women who had cesarean section after treatment with Mg++ for preeclampsia. Patients with underlying junctional disorders are more sensitive to Mg++-induced weakness. Patients with MG, and Lambert-Eaton syndrome have been reported to exacerbate in the setting of Mg++ use in spite of normal or only mildly elevated serum levels. Typically, increased MG symptoms occur with parenteral magnesium administration, but on occasion is seen with oral use.66 Therefore, parenteral Mg++ administration should be avoided and oral Mg++ preparations used with caution in patients with known junctional disease (myasthenia gravis, Lambert Eaton syndrome, botulism, etc.) (My Note: Mg makes my symptoms worse, and increased weakness). Other antibiotics including tetracyclines, sulfonamides, penicillins, amino acid antibiotics, nitrofurantoin have either been associated with occasional anecdotal reports of increased myasthenic weakness or implicated from in vitro studies to be potentially problematic. . . Fluoroquinolones have also been associated with anecdotal reports of increased weakness in myasthenic patients or implicated from in vitro studies to adversely affect neuromuscular transmission. Acute worsening of MG has been reported following administration of ciprofloxacin, a fluroroquinolone. Exacerbation of MG has been reported with use of ofloxacin, ofloxacin, and also norfloxacin. . . Clearly the issue of antibiotic effects on neuromuscular transmission is complex and poses a vexing dilemma for the clinician. Nearly every antibiotic ever studied has demonstrated some deleterious effect or has been the subject of a clinical report suggesting exacerbation of MG. (My note: might this be an argument for all Abx targeting mitochondria, and MG is really a mitochondrial disorder?) If a patient requires antibiotic treatment for an infection then the appropriate drugs should be utilized. When managing patients with junctional disease it simply behooves the clinician to remain alert to the potential for clinically significant adverse effects, especially if the patient becomes weaker in the setting of antibiotic use. “

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3238081/ Muscarinic and nicotinic acetylcholine receptor agonists and allosteric modulators for the treatment of schizophrenia. “ Furthermore, mAChR and nAChR antagonists have exacerbated existing positive and cognitive symptoms in schizophrenic patients and/or induced psychosis in normal human volunteers”.

http://ajp.psychiatryonline.org/doi/full/10.1176/appi.ajp.160.1.118 In Vivo Determination of Muscarinic Acetylcholine Receptor Availability in Schizophrenia “These results indicate a reduction in muscarinic acetylcholine receptor availability in vivo in unmedicated patients with schizophrenia, confirming results from postmortem studies and adding further evidence that the muscarinic system is involved in the pathophysiology of schizophrenia.”
Muscle-Specific Receptor Tyrosine Kinase Antibody Positive Myasthenia Gravis Current Status. “Muscle-specific tyrosine-kinase-antibody-positive myasthenia gravis (MuSK-MG) has emerged as a distinct entity since 2001. This disease has been reported worldwide, but with varying rates among patients with generalized acetylcholine-receptor-antibody-negative MG. MuSK-MG was detected in approximately 37% of generalized acetylcholine receptor antibody-negative MG. MuSK-MG patients were predominantly female with more prominent facial and bulbar involvement and more frequent crises. Disease onset tended to be earlier. Patients tended to have a relatively poor edrophonium response but showed prominent decrement in the repetitive nerve stimulation test in the facial muscles. Patients were more likely to display poor tolerance of, or a lack of improvement with, anticholinesterase agents. Somewhat better response was observed with steroids and plasma exchange. Most were managed successfully with aggressive immunomodulatory therapies, although a higher proportion of MuSK-MG patients had a refractory course when compared with other forms of generalized MG.”

Effects of Ingesting Soy or Egg Lecithins on Serum Choline, Brain Choline and Brain Acetylcholine1 (This study and next one: important if ACh homeostasis disruption is an issue in FQT)

Brain Acetylcholine: Control By Dietary Choline

A selective allosteric potentiator of the M1 muscarinic acetylcholine receptor increases activity of medial prefrontal cortical neurons and restores impairments in reversal learning (BQCA – quinolone – binds to muscarinic receptor)

Selective activation of the M1 muscarinic acetylcholine receptor achieved by allosteric potentiation

Expression of olfactory receptor genes in the mouse cornea (muscarinic receptors in olfaction)

Human tenocytes are stimulated to proliferate by acetylcholine through an EGFR signalling pathway

B-cell autoepitopes on the acetylcholinesterase-homologous region of human thyroglobulin: association with Graves' disease and thyroid eye disease.

Antibodies to acetylcholinesterase cross-reacting with thyroglobulin in myasthenia gravis and Graves's disease.

Thyroid function in patients with Alzheimer's disease treated with cholinesterase inhibitors.

Acetylcholine and norepinephrine: compared actions thyroid metabolism. (Acetylcholine, like norepinephrine, as shown previously, stimulated iodide organification by mouse thyroids in vitro, while at the same time it inhibited TSH)
The adrenergic and cholinergic innervation of the thyroid chicken gland.

A Comparison of Epitope Repertoires Associated with Myasthenia Gravis in Humans and Nonhuman Hosts

The Cholinesterase-like Domain is Required For Folding and Secretion of Thyroglobulin

Cholinesterase

Mitochondria express several nicotinic acetylcholine receptor subtypes to control various pathways of apoptosis induction

Acetyl CoA from mitochondria

Muscarinic receptor agonists and antagonists: effects on ocular function

Muscarinic receptor agonists and antagonists: effects on cardiovascular function

Muscarinic agonists and antagonists: effects on gastrointestinal function

Muscarinic receptor subtypes in the alimentary tract

Muscarinic agonists and antagonists: effects on the urinary bladder

Muscarinic receptor antagonists: effects on pulmonary function
Muscarinic receptor subtypes in neuronal and non-neuronal cholinergic function

Muscarinic receptor subtypes are differentially distributed in the rat cochlea

The plantaris tendon in association with mid-portion Achilles tendinosis: tendinosis-like morphological features and presence of a non-neuronal cholinergic system. “The tendon cells showed a distinct immunoreaction for the acetylcholine (ACh) -producing enzyme choline acetyltransferase (ChAT). Frequent fibroblasts were found in the loose connective tissue and these cells also showed a marked ChAT immunoreactions”.

Presence of a non-neuronal cholinergic system and occurrence of up- and down-regulation in expression of M2 muscarinic acetylcholine receptors: new aspects of importance regarding Achilles tendon tendinosis (tendinopathy). “The presumed local production of acetylcholine (ACh), as evidenced by immunoreactivity for ChAT and VACHT and the detection of ChAT mRNA, appears to evolve in response to tendinosis. These observations are of importance because of the well-known vasoactive, trophic, and pain-modulating effects that ACh is known to have and do unexpectedly establish the presence of a non-neuronal cholinergic system in the Achilles tendon.”

New insight into the non-neuronal cholinergic system via studies on chronically painful tendons and inflammatory situations

The non-neuronal cholinergic system of human skin

The cholinergic 'pitfall': acetylcholine, a universal cell molecule in biological systems, including humans

Thymus acetylcholinesterase activity is reduced in mice with congenital muscular dystrophy

Quantification of acetylcholinesterase-positive structures in human thymus during development and aging

Acetylcholinesterase in human thymus cells

Acetylcholinesterase at muscle-tendon junctions during postnatal development in rats

Immunological cross-reactivity between electric-eel acetylcholinesterase and rat-tail-tendon collagen

Effect of thyroid hormones on acetylcholinesterase mRNA levels in the slow soleus and fast extensor digitorum longus muscles of the rat

References 3

http://www.ncbi.nlm.nih.gov/pubmed/6201579  Inhibition of acetylcholine receptor synthesis by thyroid hormones

http://www.jbc.org/content/284/19/12752.full  The Cholinesterase-like Domain, Essential in Thyroglobulin Trafficking for Thyroid Hormone Synthesis, Is Required for Protein Dimerization


http://umaryland.pure.elsevier.com/en/publications/acetylcholinesterase-antibodies-and-thyroid-autoimmunity(80e516eb-07e0-4a03-b010-28b6b87240e0).html  Acetylcholinesterase antibodies and thyroid autoimmunity

http://www.pnas.org/content/95/17/9909.full.pdf  A single amino acid change in the acetylcholinesterase-like domain of thyroglobulin causes congenital goiter with hypothyroidism in the cogycog mouse: A model of human endoplasmic reticulum storage diseases

http://www.spandidos-publications.com/mmr/11/2/775  Effects of thyroxine and donepezil on hippocampal acetylcholine content, acetylcholinesterase activity, synaptotagmin-1 and SNAP-25 expression in hypothyroid adult rats