Catechol-O-methyltransferase

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Catechol-*O*-Methyltransferase

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AQ1
AQ2

Synonyms

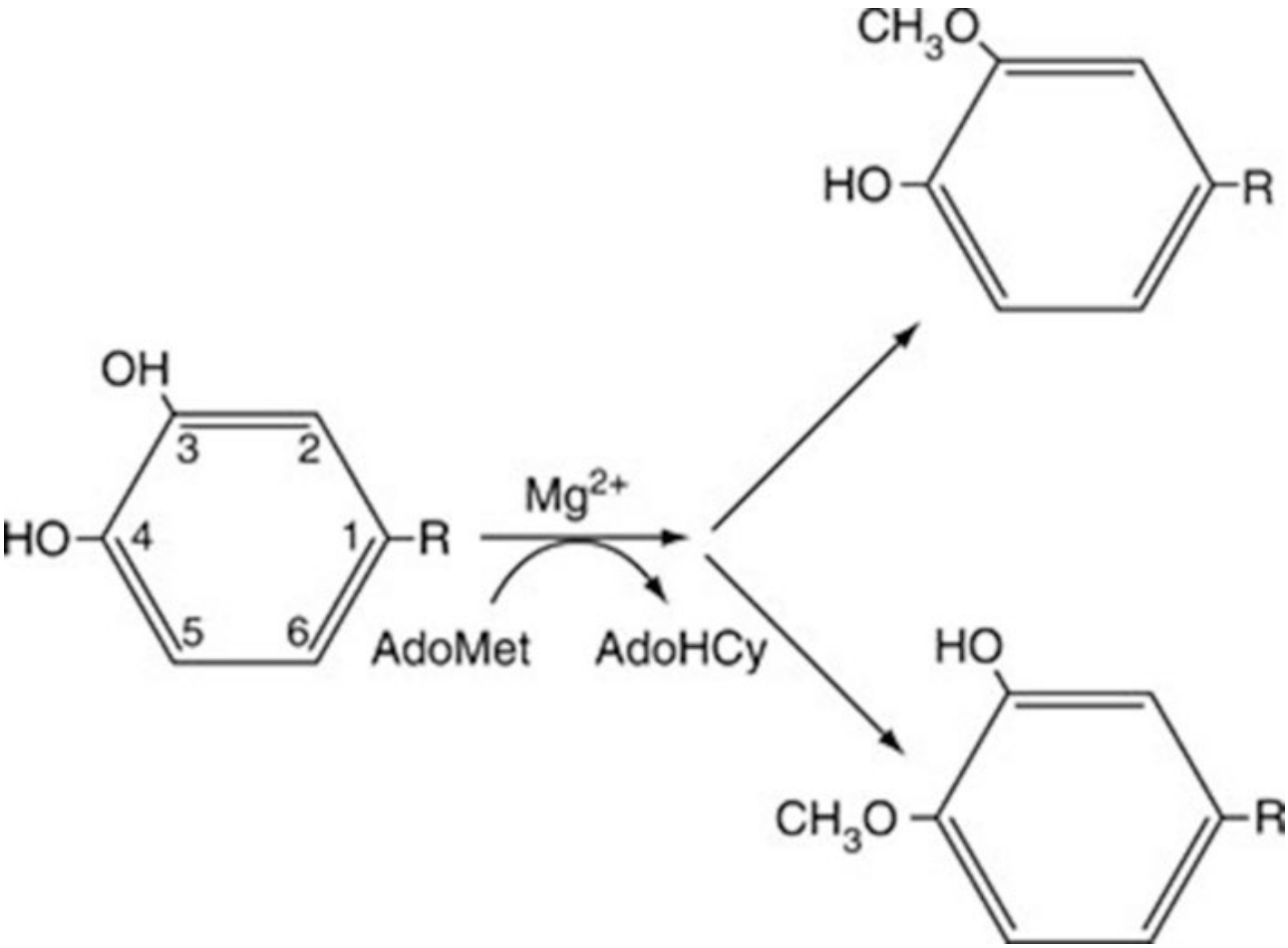
COMT; COMTase; EC 2.1.1.6

Definition

Catechol-*O*-methyltransferase (COMT) is a widespread enzyme that catalyzes the transfer of the methyl group of *S*-adenosyl-L-methionine (AdoMet) to one of the phenolic group of the catechol substrate (Fig. 1). High COMT activity is found in the liver, kidney, and gut wall (Guldberg and Marsden 1975; Männistö and Kaakkola 1989). A single *COMT* gene codes for two separate enzymes, soluble (S-COMT) and membrane-bound (MB-COMT) forms. S-COMT contains 221 amino acids. MB-COMT has an additional amino-terminal extension of 43 (rat) or 50 (man) amino acids. The hydrophobic 17 and 24 amino acid residues in rat and man, respectively, form an α-helical transmembrane domain that serves as a membrane anchor; otherwise the two proteins are similar. MB-COMT is associated with intracellular membranes, not with cell membranes. Also S-COMT is strictly intracellular locating either in cytoplasm or nucleus. Synthesis of recombinant S-COMT in *Escherichia coli* and MB-COMT in insect cells, using baculovirus vectors, has helped to clarify the biochemistry, physiology, and pharmacology of COMT (Männistö and Kaakkola 1999). The active site of COMT consists of the AdoMet-binding domain and the catalytic site. S-COMT is abundant in peripheral tissues, while MB-COMT prevails in the brain. The catalytic site is formed by a few amino acids that are important for the binding of the substrate, water, and Mg^{2+} and for the catalysis of *O*-methylation. The Mg^{2+}, which is bound to COMT only after AdoMet binding, improves the ionization of the hydroxyl groups. The lysine residue (Lys144), which accepts the proton of one of the hydroxyls, acts as a general catalytic base in the nucleophilic methyl transfer reaction. Mice lacking totally COMT (knockout mice) or only S-COMT or MB-COMT have been developed. These animals breed quite normally suggesting that COMT is not a vital enzyme. Interestingly, MB-COMT-deficient male mice exhibit schizophrenia-associated behavioral abnormalities such as aggressive behavior and reduced prepulse inhibition. Both male and female mice move normally, but they are sensitized to acute pain and have impaired short-term memory. It appears that of the two COMT isoforms, MB-COMT is critical for normal behavior, and its function in COMT-dependent brain areas cannot be entirely substituted by S-COMT (Männistö and Kaakkola 1999; Tammimäki et al. 2016).

Fig. 1

The basic function of COMT. Enzymatic *O*-methylation of the catechol substrate to 3-methoxy (major route) or 4-methoxy (minor route) products in the presence of Mg^{2+} and *S*-adenosyl-methionine (AdoMet)



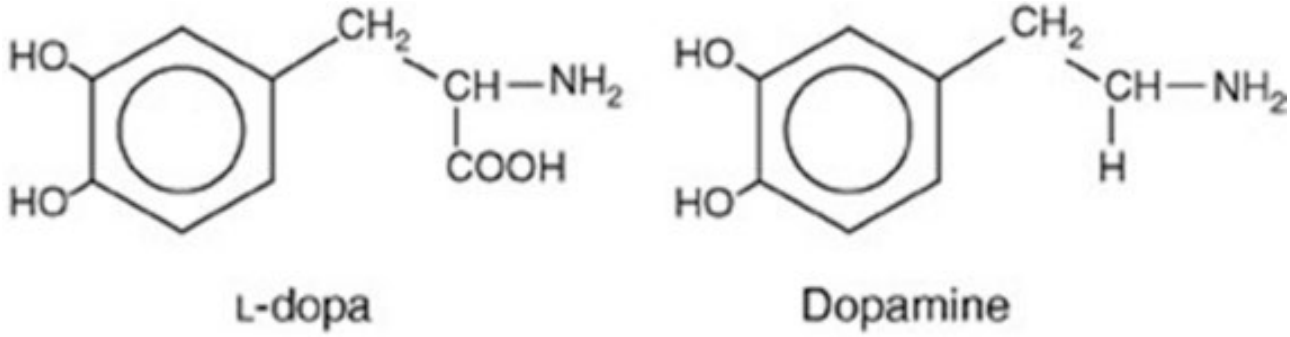
Mechanism of Action

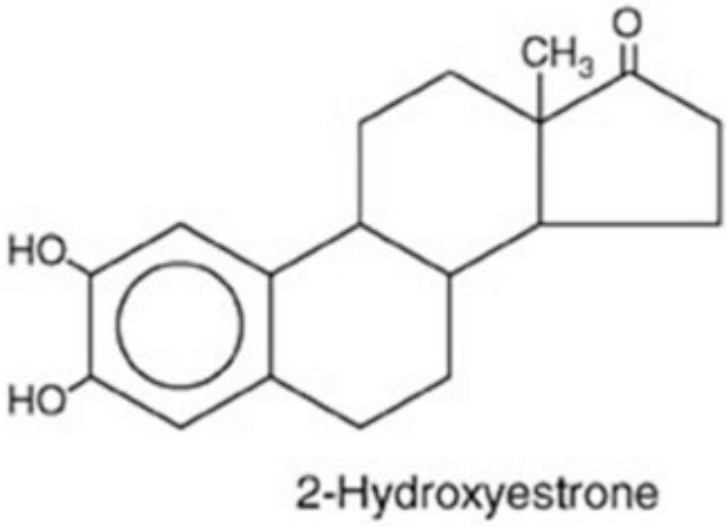
COMT *O*-methylates catecholamines and other compounds having a catechol structure including catecholoestrogens (Fig. 2). The two isoforms of COMT may have distinct roles: MB-COMT, a high-affinity isoform of COMT, is supposed to be partially responsible for the termination of dopaminergic and noradrenergic synaptic neurotransmission. S-COMT, on the other hand, is a high capacity enzyme isoform being mainly responsible for the elimination of biologically active or toxic, particularly exogenous, catechols and some hydroxylated metabolites. During the first trimester of pregnancy, COMT present in the placenta protects the developing embryo from hydroxylated compounds. COMT also acts as an enzymatic detoxicating barrier between the blood and other tissues, shielding against the detrimental effects of hydroxylated xenobiotics. COMT may serve some unique or indirect functions in the kidney and intestine tract by modulating the dopaminergic tone. The same may be true in the brain: COMT activity may regulate the amounts of active dopamine particularly in frontal cortical areas of the brain and therefore be associated with mood and other mental processes. COMT has several genetic one-nucleotide polymorphisms of which the most important one is caused by a change of valine amino acid to methionine leading to thermolability even at +37 °C and a significant decrease of COMT activity. Low COMT activity is connected to improved cognitive functions, probably due to increased dopaminergic activity. However, from population studies there is some evidence that certain psychiatric illnesses (e.g., schizophrenia, rapidly fluctuating depression) and

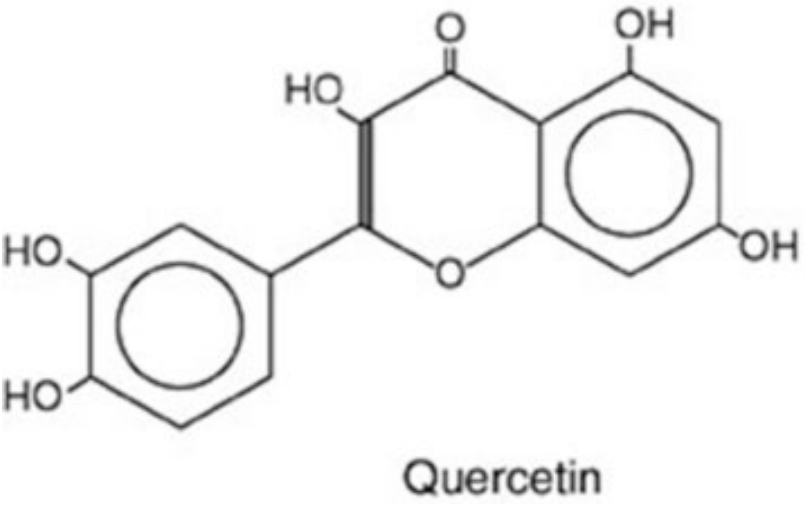
even breast cancer in postmenopausal women may be slightly increased in people having low COMT activity (Männistö and Kaakkola 1999).

Fig. 2

Some substrates of COMT







COMT Inhibitors

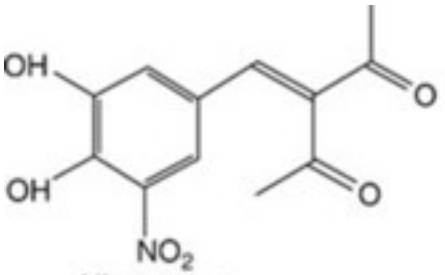
Early COMT inhibitors, like gallates, tropolone, and U-0521 (3′,4′-dihydroxy-2-methyl-propiophenone), have IC_{50} and K_i values in the micromolar range or higher but may still

be practical in vitro tools. However, owing to unfavorable pharmacokinetics and toxicity, their clinical use is not possible (Guldberg and Marsden 1975).

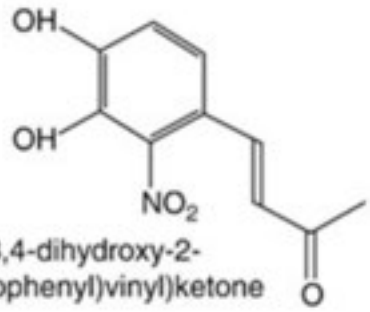
First second-generation COMT inhibitors were developed by three laboratories in the late 1980s. Apart from CGP 28014, nitrocatechol is the key structure of the majority of these molecules (Fig. 3). The current COMT inhibitors can be classified as follows: (i) mainly peripherally acting nitrocatechol-type compounds (entacapone, nitecapone, BIA 3–202, opicapone) (ii) broad-spectrum nitrocatechols having activity both in peripheral tissues and the brain (tolcapone, Ro 41–0960, dinitrocatechol, vinylphenylketone), and (iii) atypical compounds, pyridine derivatives (CGP 28014, 3-hydroxy-4-pyridone and its derivatives), some of which are not COMT inhibitors in vitro but inhibit catechol *O*-methylation by some other mechanism. The common features of the new compounds are excellent potency, low general toxicity, and activity through oral administration. Their biochemical properties have been fairly well characterized. All nitrocatechols are fast acting, reversible, but tight-binding enzyme inhibitors. The extra long-lasting COMT inhibition of opicapone can be explained by its particularly tight binding. Most of these compounds have an excellent selectivity in that they do not affect any other enzymes studied (Männistö and Kaakkola 1989, 1999; Katsaiti and Nixon 2018).

Fig. 3

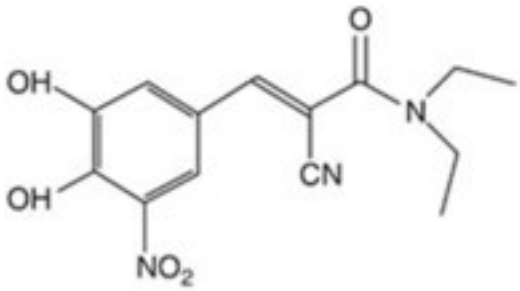
Chemical structures of some inhibitors of catechol-*O*-methylation



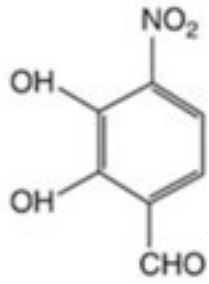
Nitecapone



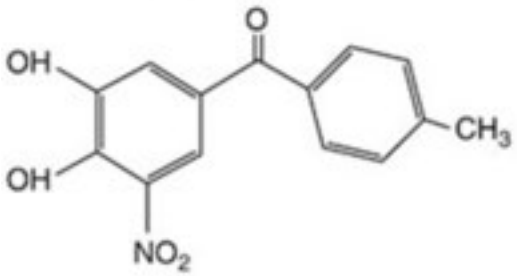
2-(3,4-dihydroxy-2-nitrophenyl)vinyl)ketone



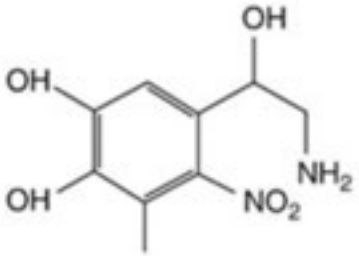
Entacapone



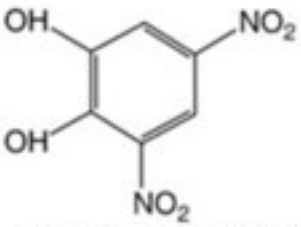
Dihydroxynitrobenzaldehyde



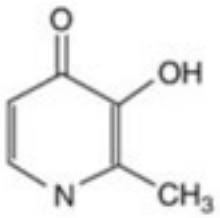
Tolcapone



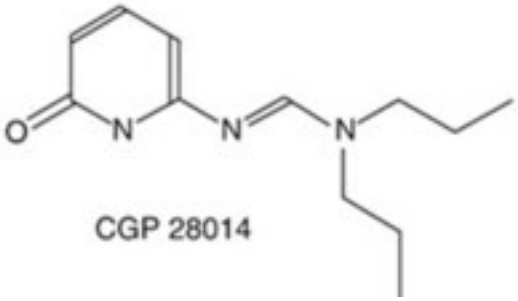
6-Nitronoradrenaline



Dinitrocatechol (OR-486)



1,2-Dihydroxyl-3-hydroxypyridine-4-one



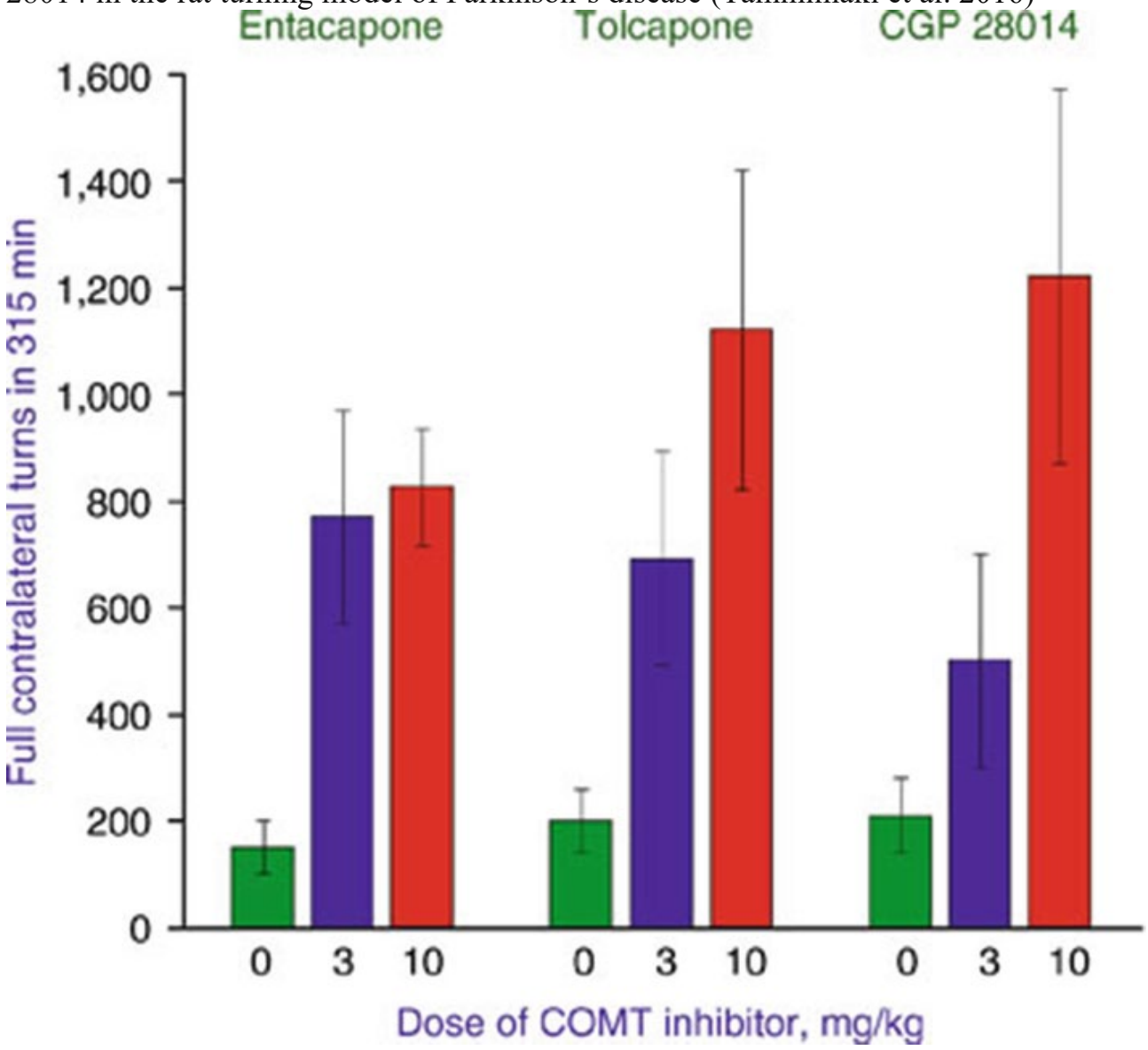
CGP 28014

AQ3
AQ4

Tolcapone, Ro 41–0960, and opicapone are longer acting than entacapone and nitecapone in in vivo studies in rats and man. All types of COMT inhibitors prolong the L-dopa-induced turning behavior of rats having unilateral nigral lesions (Fig. 4). This has generally been used as a reliable rat model of Parkinson's disease. It is noteworthy that the peripherally acting compounds entacapone and opicapone are practically as effective as the broad-spectrum compound tolcapone. This suggests that the majority of the beneficial action is peripheral in origin, evidently through enhanced bioavailability of L-dopa.

Fig. 4

Rat model of Parkinson's disease. Comparison of entacapone, tolcapone, and CGP 28014 in the rat turning model of Parkinson's disease (Tammimäki et al. 2016)



Clinical Use (Including Adverse Effects)

The main clinical use of COMT inhibitors is as adjunct (or additional adjunct) in the therapy of Parkinson's disease. The standard therapy of Parkinson's disease is oral L-dopa (as a drug levodopa) given with a dopa decarboxylase (DDC) inhibitor (e.g., carbidopa and benserazide), which does not reach the brain. When the peripheral DDC is

inhibited, the concentration of 3-*O*-methyldopa (3-OMD), a product of COMT, in plasma is many times that of L-dopa. Since the half-life of 3-OMD is about 15 h, compared to about 1 h for L-dopa, the concentration of 3-OMD remains particularly high during chronic therapy, especially if new slow release levodopa preparations are used. A triple therapy (L-dopa plus DDC inhibitor plus COMT inhibitor) will evidently substitute the present double therapy in the coming years. A fixed combination preparation containing all three active drugs is indeed getting very popular worldwide. COMT inhibitors rescue L-dopa and improve the brain entry of L-dopa by decreasing 3-OMD formation in peripheral tissues. The dose of L-dopa could be decreased, compared with the present combination therapy. Dose interval of L-dopa could also be prolonged. Further, COMT inhibitors should decrease fluctuations of dopamine formation in the brain.

Clinical studies, available only for entacapone, tolcapone, and opicapone, support preclinical findings. A dose-dependent (100–800 mg) inhibition of the COMT activity of the erythrocytes can be seen after entacapone and tolcapone. However, effective and sufficient dose levels of both entacapone and tolcapone, given concomitantly with L-dopa and DDC inhibitors to patients with Parkinson's disease, appear to be 100–200 mg. However, the treatment strategies of entacapone and tolcapone differ: entacapone is a short-acting compound that is given with each dose of L-dopa, and COMT activity may even recover between the doses. Tolcapone, as a longer-acting compound, is given three times a day, and the aim is to keep COMT inhibited most of the time. Opicapone is so long-acting that it is given only once a day (Männistö and Kaakkola 1989, 1999; Katsaiti and Nixon 2018).

Since several adrenergic drugs, having a catechol structure, are also COMT substrates, it is possible to prolong or even potentiate in some cases their actions by COMT inhibitors. Such drugs include bronchodilating compounds (adrenaline, isoprenaline, rimiterol), dopamine agonists (dobutamine, fenoldopam, apomorphine), and antihypertensive drugs (α-methyldopa). It is possible to potentiate interactions with endogenous catecholamines during stress and exercise and adverse drug interactions with, e.g., exogenous noradrenaline and the drugs mentioned above. Fortunately, interaction studies in animals and man have not been able to substantiate this threat. Evidently, the capacity of S-COMT in the peripheral tissues is so high that only a minor general COMT inhibition can ever been achieved. Estrogens are easily hydroxylated to catecholoestrogens, which serve as COMT substrates. The consequence of preventing the major metabolic pathway of catecholoestrogens by COMT inhibitors requires further studies; it is possible that quinone-forming pathways are activated (Männistö and Kaakkola 1989, 1999).

AQ5

In patients having Parkinson's disease, both entacapone and tolcapone potentiate the therapeutic effect of L-dopa and prolong the daily ON time by about 1 h. In the clinic, COMT inhibitors have been well tolerated, and the number of premature terminations has been low. In general, the incidence of adverse events has been higher in tolcapone-treated patients than in entacapone-treated patients. The main events have comprised of dopaminergic and gastrointestinal problems (Männistö and Kaakkola 1989, 1999; Katsaiti and Nixon 2018).

Dopaminergic overactivity causes an initial worsening of levodopa-induced dyskinesia, nausea, vomiting, orthostatic hypotension, sleep disorders, and hallucinations. Tolcapone has been associated with diarrhea in about 16–18% of cases and entacapone in less than 10% of cases. Diarrhea has led to discontinuation in 5–6% of patients on tolcapone and in 2.5% of those on entacapone. Urine discoloration to dark yellow or orange is related to the color of COMT inhibitors and their metabolites. Elevated liver transaminase levels are reported in 1–3% of patients treated with tolcapone but very rarely, if at all, in patients treated with entacapone or opicapone. Three cases of acute, fatal fulminant hepatitis have been described in association of tolcapone where more than 100,000 patients have been treated. In addition, a few potentially fatal neurological adverse reactions, including neuroleptic-like malignant syndrome, have been described. Because of these serious adverse drug reactions, tolcapone marketing was temporarily suspended in Europe and Canada in 1999. Now tolcapone is again available in most markets, but certain precautions and a regular follow-up of liver function need to be obeyed. So far, no restrictions of the use of entacapone and opicapone have been proposed (Männistö and Kaakkola 1989, 1999; Katsaiti and Nixon 2018).

Cross-References

Anti-Parkinson Drugs
Synaptic Transmission
α-Adrenergic System
β-Adrenergic System

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