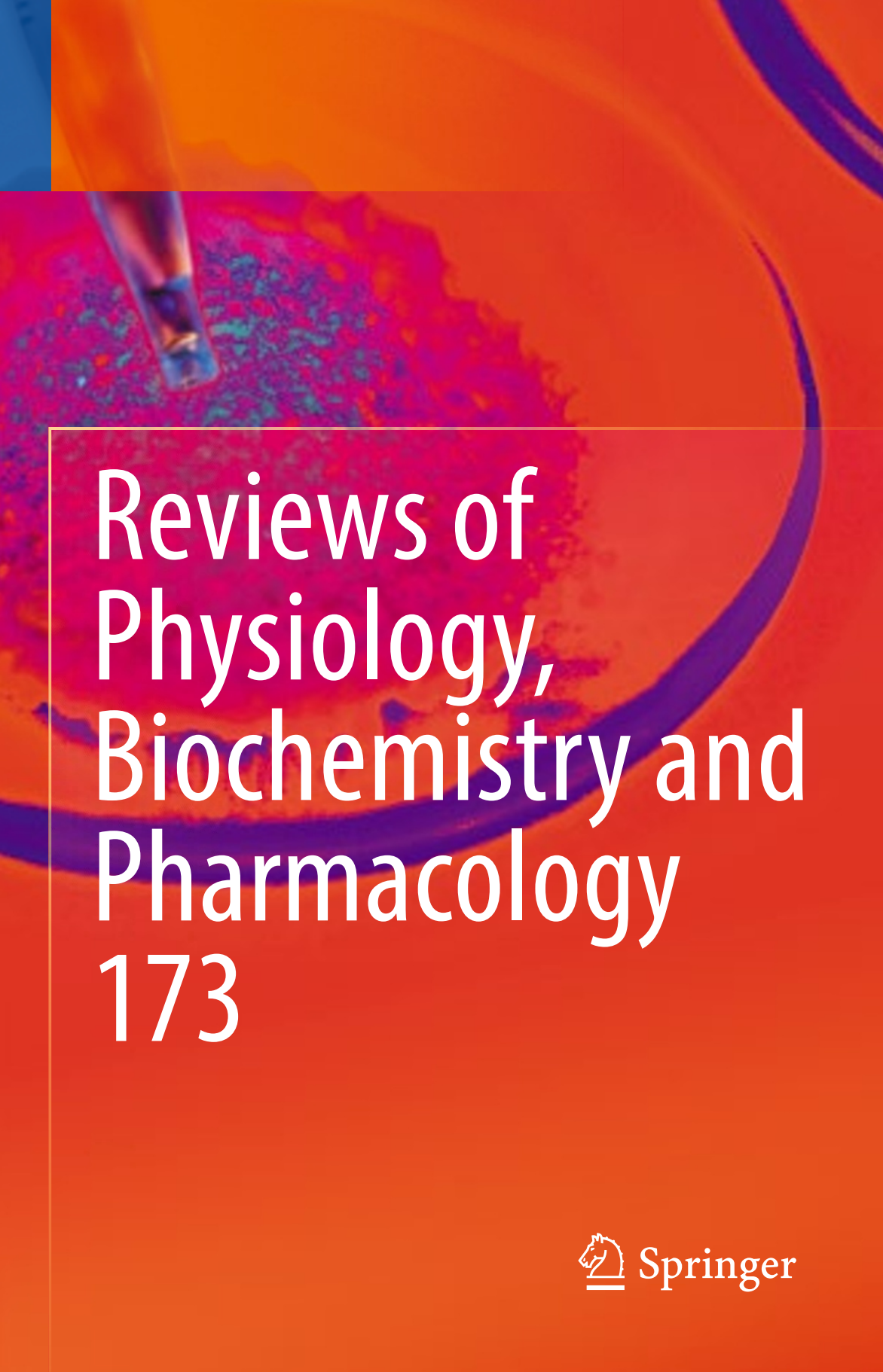
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Catechol-*O*-Methyltransferase (COMT): An Update on Its Role in Cancer, Neurological and Cardiovascular Diseases

Pedro Bastos, Tiago Gomes, and Laura Ribeiro

Abstract Catechol-*O*-methyltransferase (COMT) is an enzyme that catalyses the methylation of catechol substrates, classically in catecholamine metabolism, but also acting upon other substrates such as oestrogen and polyphenols. Although its classical function has been established for more than five decades, an ever expanding COMT role in other pathways and diseases has become a subject of active study in recent years. The most highlighted domains are related with COMT involvement in neuropsychiatric disorders and its role in the neurobiology of cognition, behaviour, emotions, pain processing and perception, sleep regulation, addictive behaviour and neurodegeneration. Nonetheless, great attention is also being devoted to a possible COMT contribution to the development of cardiovascular disorders and hormonally influenced diseases, including cancer. This review aims to update the role of COMT function and its involvement in cardiovascular and neurological disorders.

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Keywords Cancer • Cardiovascular • COMT • Neurodegeneration • Polymorphisms • Psychiatric disorders

Contents

1 Introduction

It was in 1958 that Axelrod et al. first identified and described the properties of the enzyme responsible for the *O*-methylation of catecholamines (CA) (Axelrod and Tomchick 1958). They were prompted by findings of *O*-methylated catechols in the urine of pheochromocytoma patients (Axelrod et al. 1958) and of exogenously administered CA (Axelrod and Tomchick 1958), suggesting another pathway for CA inactivation besides deamination.

Catechol-*O*-methyltransferase (COMT: EC 2.1.1.6) is an enzyme that in the presence of magnesium (Mg^{2+}) catalyses the transference of a methyl group from *S*-adenosyl-L-methionine (SAM) to a catechol substrate with *O*-methylated catechol and *S*-adenosyl-L-homocysteine (SAH) as reaction products (Männistö and Kaakkola 1999).

As a ubiquitous enzyme COMT has been found in most studied organisms across phylogenetic levels, including yeasts, plants, insects, fish, amphibians, birds and all studied mammals (Bonifacio et al. 2007; Lundström et al. 1995), stating its evolutionary and physiological relevance.

In humans, besides its role in CA catabolism COMT has been implicated in the inactivation of catecholoestrogen (CE) (Worda et al. 2003), catechol-containing xenobiotics, such as catechins and bioflavonoids (Zhu et al. 2000, 2001), and indole intermediates from melanin metabolism (Smit and Pavel 1995). COMT tissue distribution and substrate specificity support a putative protective role as an enzymatic barrier against exogenous catechols by preventing their oxidation to *o*-quinones and the formation of electrophiles (Smit and Pavel 1995; Weisz et al. 2000; Zahid et al. 2007). The catechol *O*-methylation seems to decrease the

tendency for redox cycling (Zhu et al. 1994) and to increase lipophilicity facilitating the transmembrane transport out of the cell (Smit and Pavel 1995). In addition, COMT is of great pharmacological significance, being involved in the metabolism of catechol-containing drugs such as L-DOPA, dobutamine, carbidopa, isoprenaline, benserazide, rimiterol, α-methyldopa and apomorphine, used in the treatment of asthma, hypertension and Parkinson's disease (Øverbye and Seglen 2009; Männistö and Kaakkola 1999).

COMT is strictly intracellular with two known isoforms, one soluble in the cytoplasm (soluble COMT: S-COMT) and one associated to membranes (membrane bound COMT: MB-COMT) (Huh and Friedhoff 1979; Ulmanen et al. 1997). Although these isoforms share several biochemical properties, differences are observed regarding molecular weight, cellular location, substrate specificity, kinetics and preferential position of methylation (Lundström et al. 1995). An alternative nomenclature based on the size of the isoforms has been proposed, designating S-COMT as small (S) and MB-COMT as large (L) (Øverbye and Seglen 2009).

In mammals, COMT is coded by a single gene, which in the human species is located in the band q11.21 of chromosome 22 (Tenhunen et al. 1994). The human gene has 6 exons (Fig. 1), being the first two non-coding, and presents two partially overlapping open reading frames of 663 bp and 813 bp for S- and MB-COMT (Tenhunen et al. 1994), respectively. The 5′ distal promoter (P2) regulates the synthesis of a 1.5 kb mRNA and the proximal promoter (P1), positioned between the MB- and S-COMT initiation codons in the third exon, regulates the synthesis of a 1.3 kb transcript (Lundström et al. 1995). Both transcripts share the same termination codon (TGA) in +814 of the sixth exon (Tenhunen et al. 1994). Due to a less favourable location of the MB-COMT AUG initiation codon and the occurrence of a leaky scanning mechanism, the larger mRNA has the ability to originate both COMT isoforms with translation most frequently commencing in the S-COMT AUG initiation codon (Tenhunen et al. 1994; Lundström et al. 1995).

The variable expression of COMT isoforms across different tissues and cell lines suggests that tissue specific transcription factors regulate the expression (Tenhunen

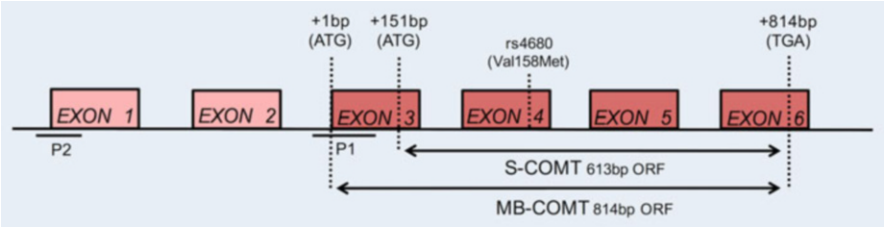

Fig. 1 Scheme of the human COMT gene structure. The human COMT gene has 6 exons, being the two most 5′ non-coding. The expression is controlled by two promoters, the P2 distal promoter regulating the synthesis of a 1.5 kb mRNA and the P1 proximal promoter regulating the synthesis of a 1.3 kb mRNA. The initiation codons for both isoforms are located in the third exon, MB-COMT (+1 bp) and S-COMT (+150 bp). The gene has a single translation termination codon (TGA) in the position +814 of the sixth exon. The two open reading frames (ORF's) of 663 and 813 bp are partially overlapping

et al. 1994; Männistö and Kaakkola 1999). Progesterone was shown to induce a distinct tissue specific effect on COMT expression via activation of one of the two progesterone receptor isoforms PR-A or PR-B (Salama et al. 2007; Jiang et al. 2003).

Both COMT promoters have oestrogen and glucocorticoid response elements that intricately regulate expression. Progesterone and dexamethasone are known to upregulate expression in leiomyoma cells (associated with PR-A) (Salama et al. 2006a) while progesterone and oestrogen downregulate expression in breast cancer cell lines (associated with PR-B) (Salama et al. 2007).

Several sequences upstream to the MB-COMT initiation codon represent potential targets for the Sp1 transcription factor and are probably responsible for the basic activity of the promoter (Tenhunen et al. 1994). In astrocytes, activation of NF-κB and p65 binding seems to downregulate the P2 promoter (Tchivileva et al. 2009; Hartung et al. 2015) and 17-β-estradiol shows a similar action in oestrogen receptor-positive human breast carcinoma (MCF-7) cells, both through the receptor's CCAAT/enhancer binding protein sites (Xie et al. 1999) and via oestrogen response elements (Xie et al. 1999; Jiang et al. 2003). No effects on COMT mRNA levels were observed after treating a glial cell line with 17-β-estradiol, supporting a tissue specific regulation mechanism (Jiang et al. 2003). In male rats, exogenous estradiol did not change COMT protein levels in the liver and frontal cortex, but decreased protein expression in the kidney and prefrontal cortex and increased COMT protein levels in the hippocampus, cerebellum and prostate (Schendzielorz et al. 2011). A positive regulation by insulin, dihydrotestosterone and *trans* retinoic acid was observed for the P1 promoter (Salih et al. 2008a). Due to the presence of a CArG box in the promoter, COMT has been identified as a transcriptional target for myocardin-related transcription factors (MRTFs), with the activation occurring through histone acetyltransferase p300 recruitment by megakaryoblastic leukemia 1 (MKL1) (Liu et al. 2013). Possible targets for p53 and for the transcription factors AP-2, NF-IL6, HNF-4, Ets-1 and NF-D have also been described (Tchivileva et al. 2009; Wang et al. 2001; Tenhunen et al. 1994). Several CpG islets have been found in the 5′ upstream region and their methylation was shown to silence MB-COMT expression (Sasaki et al. 2003). Due to the downregulation exerted by oestrogen, women have around 30% lower COMT activity than men (Harrison and Tunbridge 2008; Tenorio-Laranga et al. 2009).

1.1 Enzyme Structure and Kinetics

The enzyme consists of a typical methyltransferase topology with 8 α-helixes surrounding 7 β-sheets with the sixth sheet in antiparallel sense (Tsuji et al. 2009). The active site is located on the enzyme external surface and comprised of two distinct parts, a deeper region for SAM binding and a catalytic one for substrate binding where the Mg^{2+} ion occupies the central position (Männistö and Kaakkola 1999). In this S_N2 transfer mechanism, SAM binds first, followed by Mg^{2+} and last by the catechol substrate. After the reaction the unmethylated product SAH is the last to dissociate (Männistö and Kaakkola 1999). It is proposed that catechol recognition