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综 述

消化道多巴胺的来源、代谢和功能

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摘 要：多巴胺(dopamine, DA)是一种广泛存在于中枢神经系统和外周组织的儿茶酚胺类神经递质，其功能越来越受到学者们的关注，尤其是近年发现DA可以调节免疫系统功能，DA与肠黏膜炎症相关疾病联系的研究成为热点。消化道是外周DA的重要来源，DA不仅产生于肠神经系统和消化道上皮等部位，而且还大量产自于肠道微生物。机体组织中DA的含量变化除了受其合成酶影响外，还受到两个重要的代谢酶——单胺氧化酶(monoamine oxidase, MAO)和儿茶酚-O-甲基转移酶(catechol-O-methyltransferase, COMT)的调控。本文主要对消化道DA的来源和功能、DA代谢酶的分布和功能进行综述。

关键词：消化道；多巴胺；单胺氧化酶；儿茶酚-O-甲基转移酶
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Source, metabolism and function of dopamine in digestive tract

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Abstract: Dopamine (DA), as a catecholamine neurotransmitter widely distributed in the central nervous system and the peripheral tissues, has attracted a lot of attention. Especially in recent years, DA has been found to regulate the function of the immune system, and the involvement of DA in the intestinal mucosal inflammation-related diseases has become a hot research topic. The digestive tract is an important source of peripheral DA, and DA is not only produced in the enteric nervous system and gastrointestinal epithelium, but also produced by intestinal microorganisms. In addition to the synthetases of DA, the DA contents in body tissues are also affected by the two kinds of metabolic enzymes, monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT). This article reviewed the sources, metabolism, and functions of DA in digestive tract, especially focusing on the distribution and function of MAO and COMT, the enzymes degrading DA.

Key words: gastrointestinal tract; dopamine; monoamine oxidase; catechol-O-methyltransferase

多巴胺 (dopamine, DA) 是一种重要的单胺类神经递质，不仅在中枢神经系统发挥调控运动、认知、情绪、记忆和奖赏等作用，在外周组织，尤其胃肠道中也发挥重要作用，包括保护胃肠黏膜[1, 2]，调节黏膜离子分泌[3, 4]，调节胃肠动力等[5–9]。近年来研究表明，DA 还具有抑制神经炎症[10]、系统性炎症[11]、胰腺炎[12]和肿瘤生长[13]等功能。除了存在于中枢神经系统和外周组织外，高浓度的 DA 在肠腔内容物中也被检测出[14]。DA 的快速降解保证了正常的突触神经传递和胃肠功能的调节。单胺氧化酶 (monoamine oxidase, MAO) 和儿茶酚 -O- 甲基转移酶 (catechol-O-methyltransferase, COMT) 是代谢 DA

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的重要生物酶，在消化道分布广泛。研究显示，炎性肠病患者结肠黏膜 DA 含量显著下降 [15–17]。DA 可以通过与自身受体结合影响结肠炎症反应，其含量变化可能是炎性肠病发展的核心因素之一 [18, 19]。因此可以代谢 DA、调控 DA 含量的 MAO 和 COMT 有可能成为治疗胃肠道功能紊乱的新靶点。本文旨在综述消化道 DA 的来源、功能，尤其代谢酶的分布和功能，为 DA 生理学、病理生理学与药理学等研究提供参考。

1 DA的合成和代谢过程

如图 1 所示，酪氨酸在酪氨酸羟化酶 (tyrosine hydroxylase，TH，合成 DA 的限速酶) 的作用下生成左旋多巴 (levodopa, *L*-DOPA)，后者经多巴脱羧酶 (DOPA decarboxylase, DDC) 脱羧生成 DA。释放到突触间隙的 DA 大部分通过高亲和力的 DA 转运体 (dopamine transporter, DAT) 重摄取到突触前神经元，少量的 DA 进入静脉系统，但 DA 不能通过血脑屏障。此外，释放的 DA 中的一小部分被 DAT 和其他低亲和力转运体，如有机阳离子转运体 1-3 (organic cation transporter 1-3, OCT 1-3)[20] 和去甲肾上腺素转运体 (norepinephrine transporter, NET) 转入神经元外组织 [21]。DA 的快速降解确保了正常的突触神经传递，对肠道运动和分泌的调节具有重要意义。MAO 和 COMT 是儿茶酚胺和单胺类递质的两个重要代谢酶，此外醛脱氢酶也参与 DA 的代谢。DA 的代谢有两条途径，一条是经过 COMT 生成 3-甲氧酪氨 (3-methoxytyramine, 3-MT)，然后由 MAO 和醛脱氢酶代谢为高香草酸 (homovanillic acid, HVA)；另一条是先经过 MAO 代谢成 3，4- 二羟基苯乙醛 (3,4-dihydroxyphenylacetaldehyde, DOPAL)，然后醛脱氢酶将 DOPAL 转化为 3，4- 羟基苯乙酸 (3,4-hydroxyphenylacetic acid, DOPAC)，再经过 COMT 生成 HVA。虽然存在不同的分解途径，但 DA 代谢的最终产物是不具有生物活性的 HVA[22]。有研究报道，神经突触周围细胞外液中的生理 DA 水平为 1 μmol/L[23, 24]，血浆中 DA 的半衰期小于 2 min，小鼠脑组织中 DA 的半衰期甚至更短 [25]，这可能是由于 DA 被 MAO 和 COMT 降解成了非活性代谢产物的缘故。

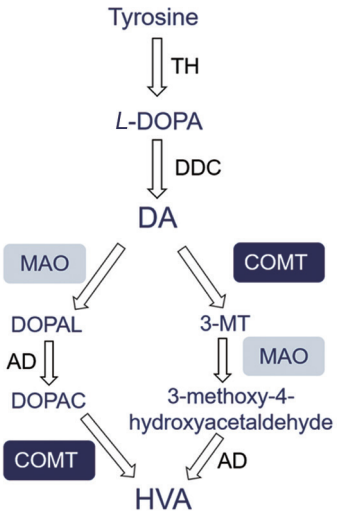

图 1. 多巴胺的合成和代谢过程

Fig. 1. The synthesis and metabolism progress of dopamine. TH: Tyrosine hydroxylase; *L*-DOPA: Levodopa; DDC: DOPA decarboxylase; DA: Dopamine; MAO: Monoamine oxidase; COMT: Catechol-O-methyltransferase; DOPAL: 3,4-dihydroxyphenylacetaldehyde; AD: Aldehyde dehydrogenase; DOPAC: 3,4-dihydroxyphenylacetic acid; 3-MT: 3-methoxytyramine; HVA: Homovanillic acid.

2 消化道DA的来源及功能

机体约 50%~70% 的 DA 来源于消化道。胃、胰腺、肠神经系统、某些免疫细胞和肠道微生物都可以合成 DA (图 2)。研究显示，胰腺 DA 的浓度为 10^{-7}~10^{-5} mol/L，小肠为 10^{-9}~10^{-5} mol/L，结肠为 10^{-8}~10^{-4} mol/L，肠道微生物也含有高浓度 DA，为 10^{-7}~10^{-4} mol/L，而循环系统中 DA 的浓度仅为 10^{-11}~10^{-8} mol/L[26]。本研究组和其他学者都发现胃壁细胞表达 TH 和 DAT，可以合成和分泌 DA[27–31]。

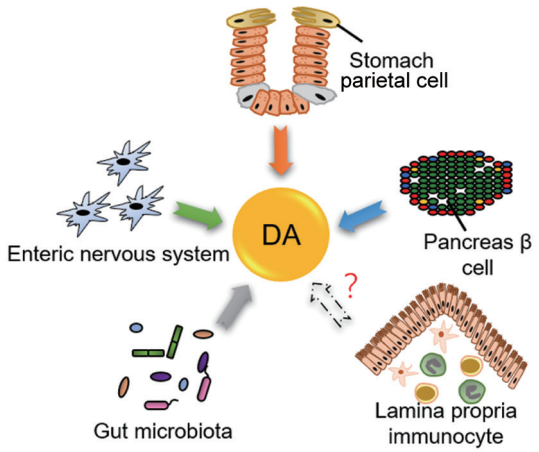

图 2. 消化道多巴胺的来源

Fig. 2. The sources of dopamine (DA) in the digestive tract. DA is generated by gastric parietal cells, neurons of the enteric nervous system, pancreas β cells, certain microorganisms, and some immune cells of the intestinal lamina propria.

在胰腺，胰岛细胞可以利用 *L*-DOPA 合成 DA，但胰岛并不表达 TH，TH 主要表达在外分泌腺泡细胞 [32, 33]。肠神经系统含有 DA 能神经元，可以合成和释放 DA[27]。研究也显示，外周血或骨髓来源的多种免疫细胞，如调节性 T 细胞 [34]、辅助 T 细胞 [35] 和树突状细胞 [36] 都表达 TH，巨噬细胞、中性粒细胞 [37] 和 B 细胞 [38] 中也含有 DA，但目前尚不明确消化道固有层的免疫细胞是否能合成 DA。DA 主要通过与受体结合来发挥作用，DA 受体是 G 蛋白耦联受体超家族的成员，包括 D_1、D_2、D_3、D_4 和 D_5 受体。在消化道，DA 与受体结合可参与多项胃肠功能的调节。(1) 调节胃酸和胃蛋白酶分泌。DA 可以抑制基础胃酸分泌 [39]，激动 D_2 受体也可抑制组胺和卡巴胆碱诱导的胃酸分泌 [40]。抑制 D_1 受体和激活 D_2 受体可显著增加胃蛋白酶分泌 [41, 42]。(2) 影响胃肠黏膜屏障。DA 通过 D_1 受体可抑制胃和十二指肠溃疡的形成，而激动 D_2 受体则具有促溃疡作用 [41]。本研究组前期研究显示，激活 D_5 受体可增加十二指肠黏膜的通透性 [1]，而激活结肠杯状细胞膜上的 D_5 受体可促进结肠黏液的合成和释放 [2]。(3) 影响上皮细胞离子分泌。DA 促进远端结肠 Cl^- 吸收与 HCO_3^- 分泌，此作用是通过 β_1 和 β_2 肾上腺素能受体介导 [3, 43]，DA 可通过 D_1 受体介导的环磷酸腺苷 (cyclic adenosine monophosphate, cAMP) 途径促进十二指肠黏膜分泌 K^+ [4]。(4) 影响胃肠动力。DA 可以抑制胃肠动力 [44–46]。本研究组前期研究也显示，DA 分别通过作用于平滑肌上的 D_2 受体和 D_1 受体抑制胃和远端结肠的动力 [6, 7]。DA 还可以调节免疫稳态。D_2 受体激动剂可通过降低血管通透性及预防血管过度渗漏减轻溃疡性结肠炎的严重程度 [18]。D_1 受体激活可升高胞内 cAMP，促进 NLRP3 炎症小体 (NLRP3 inflammasome) 泛素化和降解，抑制 NLRP3 炎症小体的活化，从而抑制脂多糖诱导骨髓源性巨噬细胞引起的系统性炎症 [11]。但腹腔注射小檗碱 (一种广泛的 DA 受体拮抗剂) 可以抑制右旋糖酐硫酸钠诱导的结肠炎小鼠肠系膜淋巴结释放干扰素 -γ 和白介素 17 [47]。虽然上述研究表明 DA 可能通过不同受体对炎症产生不一致的作用，但均提示 DA 具有免疫调节作用，关于胃肠 DA 能否直接作用于消化道的免疫细胞，从而发挥调控作用，还有待进一步研究。

近来的研究表明，肠腔内含有高浓度的 DA [14]，某些肠道细菌也可以合成 DA，如蜡样芽孢杆菌、枯草芽孢杆菌、普通变形杆菌、黏质沙雷氏菌、金黄色葡萄球菌、大肠杆菌和屎肠球菌等 [48–51]。Shishov 等在大肠杆菌培养液中检测到纳摩尔浓度的 DA[49]。Villageliu 等在体外模拟的小肠培养基中加入 *L*-DOPA，结果显示屎肠球菌可以利用 *L*-DOPA 产生 DA[51]。此外，Asano 等研究显示，无特定病原体小鼠的肠腔中存在大量游离的、具有生物活性的 DA，而无菌小鼠肠腔 90% 的 DA 呈无生物学活性的葡糖苷酸结合形式，梭状芽孢杆菌具有较高的 β- 葡萄糖醛酸苷酶活性，可显著升高无菌小鼠肠腔游离 DA 含量 [14]，提示某些细菌，特别是梭状芽孢杆菌，可能有助于肠道中产生较多的游离 DA。目前针对肠腔 DA 的功能研究较少，仅有报道肠腔内的 DA 可以促进回肠和结肠对水和电解质的吸收 [52, 53]。本研究组前期研究显示，DA 可以通过作用于结肠黏膜上皮杯状细胞上的 D_5 受体促进黏液的合成和释放 [2]，也有文献报道肠道微生物可以通过短链脂肪酸和脂多糖调节黏液合成或释放，从而影响黏液屏障 [54–57]，但肠腔内 DA 是否参与肠道菌群对黏液屏障的调节目前并不清楚。此外，在溃疡性结肠炎和克罗恩病中 DA 含量显著下降 [15, 17]，但发生机制并不清楚。最近一项研究显示，肠腔内灌流选择性 D_2 和 D_3 受体拮抗剂舒必利可以显著减轻 2，4- 二硝基苯磺酸引起的结肠炎症损伤 [19]，但此时舒必利的浓度达到毫摩尔水平，其可能会通过阻滞 DA 受体以外的药理机制发挥抗炎作用，肠腔内 DA 是否能影响炎性肠病的炎症程度仍需进一步研究。多项研究表明肠道菌群与肠炎的诱发和加剧相关 [58, 59]，微生物产生的生物活性物质可能作为宿主和细菌之间的共同语言，实现双向交流。DA 可通过 D_2 和 D_3 受体激活 T 细胞，分泌白介素 2、干扰素 -γ 和白介素 4，而服用屎肠球菌也可升高这几种炎症因子的水平 [60, 61]，DA 对炎症因子的一些影响与口服屎肠球菌的作用重叠，因此我们推测通过产生 DA 来调节炎症可能是屎肠球菌发挥作用的机制之一，但产生 DA 的益生菌，如屎肠球菌和芽孢杆菌等是否是通过产生 DA 作用于免疫细胞，从而调节肠道炎症等病理过程仍需进一步研究。

3 消化道DA代谢酶的分布和功能

3.1 MAO

MAO 是线粒体黄素蛋白酶，存在于线粒体外膜，其可以催化生物源性和外源性的胺氧化成相应

的醛。MAO 主要降解单胺类激素和神经递质，如肾上腺素、去甲肾上腺素、5- 羟色胺、酪胺、苯乙胺和 DA。在哺乳动物体内 MAO 分为两种亚型：MAO-A 和 MAO-B。它们由两个独立的基因编码，70% 的氨基酸序列具有同一性 [62]。在正常生理条件下 MAO-A 优先氧化 5- 羟色胺和酪胺，而 MAO-B 优先选择苯乙胺作为底物。作为 DA 重要的代谢酶，MAO-A 和 MAO-B 均参与代谢 DA，并在消化道组织中有广泛表达 (表 1)。

3.1.1 黏膜层的MAO

在胃体，MAO-B 存在于基底部的泌酸黏膜，并且和组氨酸脱羧酶阳性的细胞共存，可能和组胺灭活和胃酸分泌调节有关 [63]。在人十二指肠，两种亚型 MAO 在绒毛、隐窝和肌层含量都比较丰富，而黏膜下层的表达较低。MAO-A 大量存在于绒毛和隐窝，而 MAO-B 强阳性反应只存在于绒毛 [64–66]。在消化道，MAO-A 的活性约占 MAO 总活性的 80%，显著高于 MAO-B 的活性 [9, 64, 67, 68] (表 2)。MAO 可以降解摄入消化道中的膳食胺，因而对于具有潜在毒性的一些胺类物质，如酪胺等具有分解和去除毒性的作用 [69]，因此服用 MAO-A 抑制剂后，若摄入能使拟交感神经兴奋的胺类可能会产生致命的高血压危象，而 MAO-B 抑制剂无此副作用 [70, 71]。此外，结肠腔内容物 DA 的浓度略高于结肠组织，而循环系统中 DA 的浓度更低 [26]。有文献报道回肠原代上皮细胞具有 MAO 活性，可代谢外源性的 DA [68]。Caco-2 细胞系 (人肠上皮细胞系) 顶膜侧的 5- 羟色胺转运体可以转运外源性 5- 羟色胺进入细胞 [72]。本研究组前期研究显示，大鼠结肠上皮细胞的顶膜侧也表达 DAT[31]，提示肠腔内 DA 可能被 DAT 转运到结肠上皮细胞，而 DA 的代谢酶 MAO 在结肠上皮细胞也有表达，提示结肠黏膜中的 MAO 可以降解从肠腔转运到上皮细胞中的 DA，从而维持内源性 DA 的稳态。以上研究提示，消化道黏膜的 MAO 可能是抵抗外源性胺类的一道屏障。虽然 MAO 在胃肠道的表达超过了其在中枢的表达水平，但人们目前对 MAO 在消化道中的作用却知之甚少。

3.1.2 肠神经丛的MAO

MAO-A 和 MAO-B 在中枢神经系统中分布广泛，MAO-A 主要存在于儿茶酚胺能神经元，MAO-B

表1. 单胺氧化酶(MAO)-A和MAO-B在消化道的表达

Table 1. The expression of monoamine oxidase (MAO)-A and MAO-B in gut

Tissue and cell type	MAO-A protein	MAO-A mRNA	MAO-B protein	MAO-B mRNA	Species	Reference
Stomach						
Enterochromaffin-like cells			+		Rat	[63]
Duodenum						
Enterocytes of villi	+	+	+	+	Human	[64–66]
Cryptive cells	+	+	+	+		
Muscularis mucosa	+	+	+	+		
Submucosal cells	+	+	+	+		
Muscularis externa	+	+	+	+		
Brunner gland cells	–		–			
Colon						
Muscular layer	+		+		Rat	[9]
Mucosal layer	+		+			

–, not detected; +, detected.

表2. 单胺氧化酶(MAO)在消化道的活性

Table 2. The activity of monoamine oxidase (MAO) in gut

Tissue	Enzyme activity		Species	Reference
	MAO-A	MAO-B		
Jejunal epithelial cells	+	+	Rat	[68]
Caco-2 cells	+	+	Human	
Intestine	+	+	Human	[64]
Colon	+	+	Rat	[9]

+, detected.

主要存在于 5- 羟色胺和组胺能神经元，以及星形胶质细胞 [73]。本研究组之前的研究结果表明，MAO-A 和 MAO-B 在大鼠和人的结肠肌间神经丛有表达 [9](图 3)。与之前在中枢神经系统中的结果类似，MAO-B 在神经微丝 (neurofilament, NF) 阳性的神经元和胶质纤维酸性蛋白 (glial fibrillary acidic protein, GFAP) 阳性的胶质细胞中有表达，而 MAO-A 只在 NF 阳性神经元中观察到，而不表达在 GFAP 阳性胶质细胞中。大多数 GFAP 阳性细胞表达 MAO-B，但只有一小部分 NF 阳性神经元表达 MAO-B。在大鼠结肠，与 MAO-B 共存的 NF 和 GFAP 阳性细胞所占的百分比分别约为 17% 和 83%；人结肠中的比例与大鼠相似，分别约为 26% 和 75%；而在大鼠和人的结肠中 NF 阳性细胞表达 MAO-A 的百分比分别约为 52% 和 30%[9]。研究表明，中枢神经系统的 MAO-B 活性上调可升高帕金森病 (Parkinson's disease, PD) 的发病风险 [74, 75]。此外，中枢星形胶质细胞中的 MAO-B 可将 1- 甲基 -4- 苯基 -1,2,3,6- 四氢吡啶 (MPTP) 转化为毒性代谢物 1- 甲基 -4- 苯基吡啶 (MPP^+)，MPP^+ 可选择性地破坏黑质 DA 能神经元 [76]。MPTP 腹腔注射也能损毁外周 DA 能系统 [77, 78]，并诱导小鼠肠道中 TH 神经元表达和 DA 水平的选择性降低 [77, 79]。而肠胶质细胞也表达 MAO-B，提示 MPTP 在肠道中也能转化为 MPP^+，从而损伤肠道的功能，这可能是 MPTP 处理的小鼠肠道 DA 含量降低和肠动力受损的原因之一 [77–79]。本研究组前期研究也显示，MPTP 处理的小鼠胃黏膜、十二指肠、结肠 TH 的表达显著降低 [30]，提示 MAO-B 可能在全消化道的胶质细胞中都有表达。

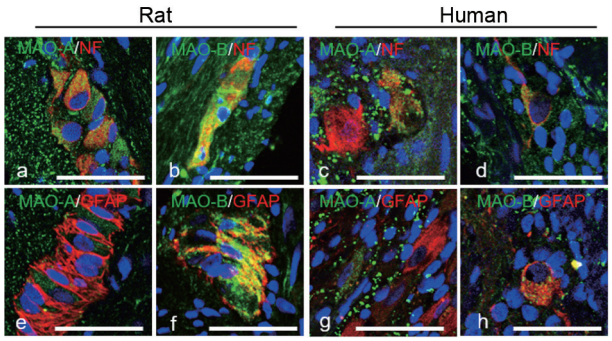

图 3. 单胺氧化酶(MAO)-A和MAO-B在大鼠和人结肠肌间神经丛和肌层的分布

Fig. 3. Distribution of monoamine oxidase (MAO)-A and MAO-B in the colonic myenteric plexus and muscle layer of rat (a, b, e and f) and human (c, d, g and h). NF, neurofilament; GFAP, glial fibrillary acidic protein. Scale bar, 50 μm.

3.1.3 消化道平滑肌的MAO

MAO-A 和 MAO-B 在十二指肠和结肠的肌层都有表达 (表 1)。本研究组研究显示，大鼠结肠肌层中 MAO-B 蛋白表达显著高于黏膜层，而 MAO-A 蛋白表达并无显著差异 [9]。平滑肌中的 MAO 可能通过影响单胺神经递质 (如 DA) 的水平影响结肠动力与转运。由于 MAO-B 抑制剂可以抑制 DA 代谢，目前 MAO-B 抑制剂已经成为治疗 PD 的重要药理学靶点，常用的药物为雷沙吉兰 (rasagiline) 和沙芬酰胺 (safinamide)。雷沙吉兰是第二代选择性、不可逆的 MAO-B 抑制剂 [80, 81]。沙芬酰胺是第三代选择性、可逆性 MAO-B 抑制剂，并且还具有抑制谷氨酸释放的作用。此外，雷沙吉兰和沙芬酰胺都具有神经保护作用 [82, 83]。在临床应用时，雷沙吉兰在 PD 早期阶段可作为单一疗法使用，缓解疾病进程，或在 PD 的晚期阶段使用，辅助 *L*-DOPA 改善运动症状 [84, 85]。当作为 *L*-DOPA 的辅助用药或与其他 PD 药物联合使用时，沙芬酰胺增加每日“打开”时间 (ON time)，即药物起效且患者症状得到控制的时间段，而不会造成运动障碍，显著改善中晚期波动性 PD 患者的运动症状和生活质量 [86]。但也有临床报道，长期联合使用 *L*-DOPA 和 MAO-B 抑制剂 (雷沙吉兰和沙芬酰胺) 后，PD 患者出现便秘症状的几率增加 [87–89]。本研究组研究显示，雷沙吉兰给药 4 周可通过抑制大鼠结肠 MAO-B 活性减少 DA 代谢，升高结肠 DA 水平，抑制结肠动力 [5–7]。DA 可以通过与其 D_1 受体结合抑制结肠动力，延长结肠转运时间 [5, 6]，通过与 D_2 受体结合抑制胃动力与胃排空 [7, 45]。这可以解释为什么长期使用雷沙吉兰的 PD 患者便秘风险可能会有增加。

3.2 COMT

COMT 在二价金属 Mg^{2+} 离子的存在下可以催化甲基基团从 S- 腺苷甲硫氨酸转移到儿茶酚胺类神经递质上，其底物包括 *L*-DOPA、DA、肾上腺素和去甲肾上腺素等。COMT 存在两个亚型：膜结合性 COMT (MB-COMT) 和可溶性 COMT (S-COMT)，两个亚型的 COMT 由同一个基因编码。S-COMT 存在于胞质溶胶中，是 COMT 的主要形式，被认为在消除外源性生物活性或毒性的儿茶酚胺和一些羟基化代谢物中扮演更重要的角色；MB-COMT 是一种微粒体蛋白，定位于粗面内质网，在儿茶酚胺生理低浓度时发挥作用，可终止 DA 和去甲肾上腺素的突触传递 [90]。因此，在肠黏膜和大脑中，COMT

也作为血液和其它组织之间的解毒屏障，屏蔽外源化学物质的有害影响[91]。

3.2.1 黏膜层的COMT

消化道上皮细胞广泛表达COMT[92, 93]（表3），如胃体、幽门、十二指肠、回肠和结肠。研究报道，胃体和幽门上皮细胞表达COMT，小鼠十二指肠上皮细胞和微绒毛中也存在COMT，但在胃肠道的内分泌细胞则并未见COMT的表达[94]。MB-COMT和S-COMT在不同区域的活性不同[68, 92]（表4）。在大鼠小肠，S-COMT是黏膜和肌层中COMT的主要形式，并且S-COMT活性在十二指肠黏膜层最高，空肠和回肠黏膜层稍低。而MB-COMT的活性在黏膜和肌层以及胃肠道的不同区域几乎相等。*L*-DOPA的主要吸收部位是十二指肠和空肠，而胃肠道黏膜中COMT的高表达和活性可能有助于儿茶酚如*L*-DOPA的代谢[92]。COMT抑制剂可防止*L*-DOPA在外周组织转化为3-O-甲基多巴，上调外周*L*-DOPA水平，因而进入到中枢的*L*-DOPA增多，DA的合成增加。此外，进入中枢的COMT抑制剂可通过降低*L*-DOPA和DA的代谢，进一步提高*L*-DOPA的利用度和DA的含量，因此COMT的抑制剂成为治疗PD患者的辅助药物，在临床上广泛应用。据报道，切除肝脏的大鼠其血浆或其他组织中3-O-甲基多巴的水平没有降低[92]，提示消化道的COMT

表3. 儿茶酚-O-甲基转移酶(COMT)在消化道的分布

Table 3. The expression of catechol-O-methyltransferase (COMT) in gut

Tissue and cell type	COMT protein	Species	Reference
Stomach			
Epithelial cells of corpus	+	Rat	[93]
Pylorus	+		
Endocrine cells	−		
Duodenum			
Epithelial cells	+	Mouse	[94]
Microvilli	+		
Ileum			
Epithelial cells	+	Rat	[93]
Colon			
Mucosal layer	+	Rat	[98]

−, not detected; +, detected.

表4. 儿茶酚-O-甲基转移酶(COMT)在消化道的活性

Table 4. The activity of catechol-O-methyltransferase (COMT) in gut

Tissue	Enzyme activity			Species	Reference
	S-COMT	MB-COMT	COMT		
Duodenum				Human	[92]
Mucosal layer	+	+			
Muscular layer	+	+			
Jejunum					
Mucosal layer	+	+			
Muscular layer	+	+			
Ileum					
Mucosal layer	+	+			
Muscular layer	+	+			
Duodenum	+	+		Rat	
Jejunum	+	+			
Ileum	+	+			
Jejunal epithelial cells			+	Rat	[68]
Caco-2 cells			−	Human	

−, not detected; +, detected.

在外源性儿茶酚的代谢中发挥着重要作用。回肠原代上皮细胞的 COMT 被证明可代谢外源性的 DA[68]，而结肠内容物含有高浓度的 DA[14]，结肠上皮细胞的顶膜侧也表达 DAT[30]，因此我们推测结肠黏膜中的 COMT 可能也参与维持内源性 DA 的稳态，降解从肠腔转运到上皮细胞中的 DA。

3.2.2 肠神经丛和平滑肌的COMT

在中枢神经系统，COMT 在神经元和神经胶质细胞中有表达，并且神经元中 COMT mRNA 水平明显高于神经胶质细胞 [95]。在人和大鼠的中脑 DA 能神经元中均检测到 COMT mRNA[95]，但 COMT 在肠神经系统中的分布目前尚未见报道，并且其在肌层的表达研究也较少。在人小肠各部位的肌层，MB-COMT 的活性相差不大，但 S-COMT 活性在十二指肠最高，其次是空肠，回肠最低 [92] 。COMT 抑制剂在临床应用时存在诱发腹泻等副作用，有时甚至发生在开始治疗后 2~4 个月 [96]。本研究组前期研究显示，COMT 抑制剂恩他卡朋可能通过促进结肠上皮细胞分泌 Cl^-，从而引起腹泻 [97]。此外，本研究组研究显示，恩他卡朋以剂量依赖性的方式抑制离体结肠纵行肌的自发收缩，这种抑制作用可被 β_2 肾上腺素受体拮抗剂阻断 67%[98]，提示恩他卡朋抑制结肠动力可能是 β_2 肾上腺素受体介导的。但 COMT 是否能通过影响单胺神经递质 (如 DA) 的水平来影响结肠动力尚未见报道。

4 小结

除中枢神经系统以外，消化道是机体 DA 不可忽视的重要来源地。消化道分布着大量的 MAO 和 COMT，对于调控消化道 DA 的含量和功能发挥着重要作用。肠道微生物可以产生 DA，许多疾病如肠易激综合征、炎症性肠病以及代谢性疾病和神经退行性疾病等均表现有肠道微生物群的改变，DA 在其中扮演何种角色，功能意义如何，这些问题有待进一步的研究。

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