基于药物转运体机制的二甲双胍体内过程研究进展

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摘要: 转运体在药物的吸收、分布以及排泄过程中发挥着重要作用。明确药物转运机制有利于提高药物安全性和有效性, 从而指导临床合理用药。二甲双胍作为 2 型糖尿病的临床一线用药, 多种转运体参与了其体内过程, 转运体表达和功能的改变直接影响其药动学和药效学。本文综述了基于药物转运体机制的二甲双胍体内过程, 这些转运体包括有机阳离子转运体 (OCTs)、多药及毒性化合物外排转运蛋白 (MATE)、质膜单胺蛋白转运体 (PMAT)、五羟色胺转运体 (SERT)、硫胺素转运体 2 (THTR-2)、肉碱/有机阳离子体 1 (OCTN1)。

关键词: 转运体; 二甲双胍; 药动学; 药物–药物相互作用; 有机阳离子转运体; 多药及毒性化合物外排转运蛋白

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Research progress of pharmacokinetics of metformin based on transporters

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Abstract: Drug transporters play vital roles in absorption, distribution and excretion of drugs. Understanding the transport activity can improve the effectiveness and safety of drugs and guide clinical rational use of drugs. Metformin is a first-line drug in the treatment of type 2 diabetes mellitus, of which the pharmacokinetics involves several transporters. The changes in expression and function of these transporters affect directly the pharmacokinetics/pharmacodynamics of metformin. This paper reviews the research progress of pharmacokinetics of metformin based on transporters, and these transporters are organic cation transporters (OCTs), multidrug and toxin extrusion proteins (MATE), plasma membrane monoamine transporter protein (PMAT), serotonin reuptake transporter (SERT), thiamine transporter 2 (THTR-2), and carnitine/organic cation 1 (OCTN1).

Key words: transporter; metformin; pharmacokinetics; drug-drug interaction; organic cation transporter; multidrug and toxin extrusion protein

二甲双胍是双胍类药物, 为 2 型糖尿病临床一线用药[1], 对于改善糖代谢和胰岛素抵抗[2]等有重要作用, 且可以保护心血管[3], 是目前唯一被糖尿病指南推荐为有明确心血管保护作用的降糖药物[4]。此外, 二甲双胍临床治疗及预防价值不断被发现, 如用于多囊卵巢综合征[5]、肥胖、非酒精性脂肪性肝病[6], 且有抗癌[7]、抗衰老[8]等疗效。二甲双胍具有显著个体差异性, 大约 30% 的患者在服用正常剂量的二甲双胍时会出现较为明显的胃肠道反应, 少数患者还会发生更为严重的乳酸性酸中毒[9]。

二甲双胍多采用口服给药, 生物利用率为 55% ± 16%, 主要通过小肠吸收。其进入人体后几乎不与血红蛋白结合, 不易被代谢, 主要以原形 (79%) 通过尿液排泄, 约 20% 可以在粪便中检测到[10], 极小部

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分 (0.11%±0.02%) 通过胆汁排泄[11]。

药物转运体在药物药代动力学过程中起到了重要作用, 与药物疗效、不良反应以及毒性等密切相关[12], 其功能的变化直接影响药物的吸收、分布、代谢和排泄[13]。二甲双胍的体内吸收、分布、排泄过程均有药物转运体的参与[14]。本文对基于药物转运体机制的二甲双胍体内过程的研究进展进行综述。

1 有机阳离子转运体

有机阳离子转运体 (organic cation transporters, OCTs) 属于 *SLC22* 基因家族, 其底物以亲水性阳离子小分子化合物为主, 在人体肝脏、肾脏和肠等器官均有表达[15]。

OCTs 在二甲双胍的吸收、组织分布过程扮演重要角色。① 在小肠部位, 由分布于肠细胞顶膜的 OCT3 负责将二甲双胍转运进入肠细胞; 而肠细胞基底侧膜的 OCT1 负责二甲双胍进一步的转运[16, 17]; 另有研究发现 OCT1 在肠细胞的顶膜侧也有分布[18]。Jensen 等[19]通过实验发现 OCT1 敲除小鼠的小肠浓度显著降低; Shirasaka 等[20]的实验结果显示, 正常小鼠的绝对生物利用度为 46.8%, OCT3 敲除小鼠绝对生物利用度显著下降至 32.6%。② 二甲双胍在肝脏的吸收主要通过位于肝细胞窦状隙膜 (基底侧膜) 的 OCT1 将其从血液中转运进入肝脏, OCT3 也有少量贡献[21]。在 OCT1 敲除小鼠体内实验中, 正常小鼠的二甲双胍肝浓度是 OCT1 敲除小鼠的 30 倍左右, 验证了 OCT1 在肝脏摄取二甲双胍过程的重要性[22]。细胞实验也显示口服降糖药瑞格列奈和罗格列酮可以通过抑制 OCT1 来显著减少二甲双胍的细胞摄取[23]。③ 肾脏中介导二甲双胍的阳离子转运体主要为 OCT2, 多位于肾小管细胞基底外侧并将二甲双胍转运进入近曲肾小管内细胞[24]。若抑制 OCT2 将减少二甲双胍的体内清除, 可能会增加二甲双胍的不良反应, 尤其是乳酸酸中毒[25]。Ding 等[26]的健康受试者实验表明, OCT 抑制剂兰索拉唑可以增加二甲双胍血浆浓度−时间曲线下面积 17%。综上所述, 临床上要尽可能避免瑞格列奈、罗格列酮和兰索拉唑以及其他可以影响 OCTs 功能的药物与二甲双胍合用, 以免影响二甲双胍的治疗效果。

OCT1 基因多态性是造成二甲双胍药效个体差异的重要因素, 如 *rs622342* 基因型影响了二甲双胍对于南印度地区二型糖尿病患者的治疗药效[27]。低活性基因型 OCT1 降低了二甲双胍在肝脏中的分布[25], 其基因变体包括: *Arg61Cys* (*181C>T*, 单核苷酸多态性 (SNP) *rs12208357*), *Gly401Ser* (*1201G>A*, SNP *rs34130495*), *Met420del* (*1256delATG*, SNP *rs72552763*) 和 *Gly465Arg* (*1393G>A*, SNP *rs34059508*)。与此相反, *622342A>C* 突变可以使二甲双胍在肝脏中的浓度升高[28]。此外, OCT1 基因多态性 *R61C(C>T)*、*G401S(G>A)*、*G465R(G>A)* 和 *M420del* 也影响了患多囊卵巢综合征的糖尿病女性患者的二甲双胍个体治疗效果[29]; 对于使用二甲双胍治疗去势抵抗性前列腺癌的患者, OCT1 的 C 等位基因与二甲双胍毒性降低有关[30]。OCT2 基因位点突变与服用二甲双胍的 2 型糖尿病患者的肾脏清除相关[31], 进而影响血浆乳酸水平和高乳酸血症的发生。有研究证实中国人群中存在 OCT2 基因多态性, 并且表明 *808G>T* 基因多态性与二甲双胍肾清除降低有关[32]。同时在群体药代动力学模型中, OCT2-*808G>T* 和 OCTN1-*917C>T* 变体显著影响二甲双胍的清除率[33]。一项中国 2 型糖尿病患者的临床研究表明, OCT2-*808G>T* 可以通过推迟二甲双胍的消除从而增强其降血糖作用[34]。此外, Song 等[35]的卵母细胞结果表明, OCT2 的 3 种基因突变型 OCT2-*T199I*、-*T201M* 和-*A270S* 可使 OCT2 对二甲双胍的摄取能力显著下降。

OCT3 的基因多态性对二甲双胍的转运也有影响。Chen 等[36]的研究发现, OCT3 *T400I (c.1199C>T)* 和 *V423F (c.1267G>T)* 变体使得二甲双胍在细胞的吸收量显著降低, 但 *T44M(c.131C>T)* 变体可以使二甲双胍在细胞的吸收量明显升高 50% 以上。临床上二甲双胍的组织分布和治疗效果有个体差异, 可用阳离子转运体的基因多态性解释[37]。

2 多药及毒性化合物外排转运蛋白

多药及毒性化合物外排转运蛋白 (multidrug and toxin extrusion proteins, MATEs) 是 *SLC47* 基因家族的一员, 底物主要为有机阳离子, 分布在肝脏和肾脏等器官, 对于二甲双胍的最终排泄过程有很大影响[38]。

研究显示, 肝脏胆小管的管腔侧有 MATE1 分布, 负责将极少部分的二甲双胍排泄进入胆汁[19]。在肾脏中, MATE1[39]、MATE2-K[40]主要表达于肾近端小管的刷状缘膜, 将二甲双胍从肾小管细胞中转运进入尿液[41]。在 MATE1 基因敲除小鼠体内, 二甲双胍血浆、肾脏组织浓度均显著升高, 尿排泄量可减少 14%[42]。Ma 等[43]通过大鼠的实验认为, 联合给予 β 受体阻断剂阿替洛尔后二甲双胍的尿排泄降低与 MATE1 的下调有关。临床健康志愿者实验表明, MATE1 抑制剂甲氧苄啶可导致二甲双胍肾清除率显著减少 (从 31～21 h^{-1}), 半衰期延长 (从 2.7～3.6 h), 导致 C_{max} 和 AUC 分别增加了 38% 和 37%[44]; 在健康

志愿者体内, MATE 抑制剂乙胺嘧啶使二甲双胍肾清除率降低了 35%, C_{max}和 AUC 均显著增加[45], 故临床上要避免甲氧苄啶、乙胺嘧啶等 MATE 抑制剂与二甲双胍的合用。

MATEs 基因变异会引起二甲双胍的临床治疗个体差异。MATE1 等位基因 *rs2252281T>C* 和 *rs2289669G>A* 患者体内二甲双胍降糖治疗效果增强; 但 MATE2 等位基因 *rs12943590G>A* 二甲双胍的降血糖活性降低[46]。需要提出的是, 携带 OCT1 (*A>C*, SNP *rs622342*) 和 MATE1 (*G>A*, SNP *rs2289669*) 基因变体的患者二甲双胍抗高血糖作用得到增强, OCT2 的 SNP *c.808* (*G>T*) (*rs316019*) 和 MATE1 的 SNP *g.-66T>C (rs2252281)* 对二甲双胍肾消除的影响会相互抵消[47]。临床上对患者的 MATEs 基因多态性应予以重视。

3 质膜单胺蛋白转运体

质膜单胺转运体 (plasma membrane monoamine transporter, PMAT) 是一种新的多特异性有机阳离子转运蛋白, 属于 *SLC29* 基因家族, 运输各种生物胺和外源性阳离子, 在人肠道有所表达, 主要分布在刷状缘侧[48]。

有研究证实 PMAT 是二甲双胍在胃肠道吸收中的主要转运体之一。Han 等[49]通过单层 Caco-2 细胞模型实验, 表明 PMAT 在二甲双胍的肠道吸收贡献率为 20%。在去极化和酸性 pH 值条件下, PMAT 介导二甲双胍转运初始速率会大大提高[50]。动力学分析表明, 二甲双胍 PMAT 介导吸收动力学具有 S 形, 猜测 PMAT 蛋白可能包含一个大的底物结合口袋, 它允许不同底物在不同的位点相互作用或多个分子同时识别同一基板[50]。但 PMAT 的基因多态性对二甲双胍药代动力学的影响未见报道。

4 五羟色胺转运体

五羟色胺转运体 (serotonin reuptake transporter, SERT) 是一种约为 630 个氨基酸残基的蛋白质, 属于 *SLC6* 基因家族[51], 是体内重要神经递质五羟色胺的转运体, 广泛分布于大脑边缘系统、胃肠道细胞膜、肥大细胞和五羟色胺能神经突触前膜上[52], 五羟色胺转运体的活性与体内部分抗抑郁症的药物药效相关[53]。

Han 等[49]的 Caco-2 细胞模型实验表明 SERT 在二甲双胍的肠道吸收贡献率为 20%。此外, Yee 等[54]研究发现, 二甲双胍是 SERT 的底物同时可以抑制 SERT, 临床上二甲双胍胃肠道不良反应的发生可能与其抑制五羟色胺的摄取有关[55]。所以在临床上要警惕由其抑制 SERT 介导的药物−药物相互作用的发生, 避免与 SERT 的底物如安非他酮、利他林和丙咪嗪等药物联合使用。

5 硫胺素转运体 2

硫胺素转运体即维生素 B1 转运体 (thiamine transporter, THTR), 属于 *SLC19* 基因家族, 底物主要为维生素 B1, 在肝、肾、小肠、胎盘和肌肉等组织广泛分布[56]。

THTR 的吸收机制是 pH 值和电化学梯度敏感[57]。Liang 等[58]利用人胚胎肾 293 细胞模型, 证实二甲双胍是 THTR-2 (*SLC19A3*) 的一种底物和抑制剂, 同时二甲双胍可以抑制硫胺素的吸收 (IC_{50} = 680 μmol·L^{-1}), 而硫胺素 (维生素 B1) 缺乏可能与乳酸酸中毒的发生有关[59]。在临床服用二甲双胍时要警惕由 THTR-2 介导的二甲双胍−药物或二甲双胍−维生素相互作用的发生。

6 肉碱/有机阳离子体 1

肉碱/有机阳离子体 1 (carnitine/organic cation 1, OCTN1) 属于 *SLC22* 基因家族, 主要在小肠刷状缘膜表达, 在气管、骨髓、肝脏、肾脏等部位有少量表达[60]。

有研究表明 OCTN1 参与二甲双胍口服后的小肠吸收过程, 口服二甲双胍 (175 mg·kg^{-1}) 后最大血浆浓度在 *OCTN1* 基因敲除小鼠 (*OCTN1*$^{-/-}$) 明显低于野生型小鼠[61]。Futatsugi 等[62]利用转染 HEK293 细胞实验表明 OCTN1 基因变种 *L503F* 转运二甲双胍的效率提高; 而在亚洲人和高加索人中发现的 OCTN1 基因变种 *I306T* 转运二甲双胍的效率则降低。关于 OCTN1 基因多态性对二甲双胍药效的影响尚未见报道。

7 结语

近年的研究发现, 由转运体介导的药物相互作用是导致药物不良反应的一个重要机制, 所以对于药物相互作用具体机制的研究是减少不良反应发生的重要方法之一。二甲双胍作为 2 型糖尿病临床的一线用药, 临床治疗及预防价值越来越引起重视, 其在体内的吸收、分布、排泄有多种转运体参与, 见图 1。肠道细胞 OCT1、PMAT、SERT 等多种转运体介导二甲双胍的肠吸收, 贡献比例分别为 25%、20%、20%[49]; 肝脏摄取主要由 OCT1 摄取[22], 极少量药物通过 MATE1 排到胆汁[19]; 而肾脏中则由 OCT2 摄取[24], MATE1、MATE2-K 负责外排[41], 部分主要转运体的转运参数见表 1。临床上患者在服用二甲双胍联合使用其他药物时, 可能会增加药物−药物相互作用发生的可能性, 甚至发生不良反应及毒性。因此,

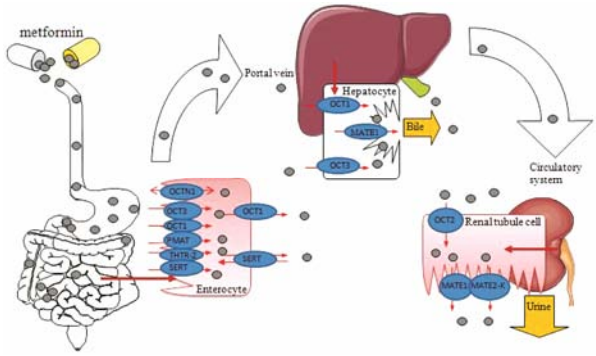

Figure 1　Pharmacokinetics process of metformin mediated by transporter *in vivo*[19, 54, 58, 61]. MATE: Multidrug and toxin extrusion proteins; OCT: Organic cation transporters; OCTN: Carnitine/organic cation; PMAT: Plasma membrane monoamine transporter; SERT: Serotonin reuptake transporter; THTR: Thiamine transporter

Table 1　Apparent affinities of transporters toward metformin

Transporter	Cell line	V_{max} /nmol·min^{-1}·mg^{-1}	K_m /mmol·L^{-1}
PMAT	MDCK	−	1.32[50]
OCT1	CHO	1.8 ± 0.1	3.1 ± 0.3[49]
OCT2	CHO	1.6 ± 0.1	0.6 ± 0.1[49]
OCT3	CHO	4.5 ± 0.2	2.6 ± 0.2[49]
SERT	CHO	−	4.0[49]
THTR-2	HEK293	−	1.15 ± 0.2[58]
MATE1	HEK293	4.5 ± 0.6	0.78 ± 0.10[39]
MATE2-K	HEK293	1.7 ± 0.3	1.98 ± 0.48[39]

阐明基于药物转运体机制的二甲双胍体内过程，将有助于促进二甲双胍临床合理用药，提高疗效和降低不良反应发生的风险。

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