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综 述

低氧对药物代谢酶和转运体的影响及其调控机制

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摘 要：低氧环境中药物在体内的代谢会受到显著影响，其中药物代谢动力学参数、药物代谢酶及转运体的表达及功能均会发生变化。研究表明机体在低氧状态下会释放一系列炎性因子对药物代谢产生调控。此外，低氧诱导因子1α (hypoxia inducible factor 1α, HIF-1α)和微小RNA (microRNA, miRNA)介导的通路均对药物代谢有调控作用。本文对低氧状态下药物代谢的变化情况及其单因素调控机制进行综述，并提出多因素调控机制的推测及展望。

关键词：低氧；药物代谢酶；转运体；调控机制
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Modulation of drug-metabolizing enzymes and transporters under hypoxia environment

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Abstract: Drug metabolism is significantly affected under hypoxia environment with changes of pharmacokinetics, expression and function of drug-metabolizing enzymes and transporters. Studies have shown that hypoxia increases the release of a series of inflammatory cytokines which can modulate drug metabolism. Besides, both hypoxia inducible factor 1α (HIF-1α) and microRNA-mediated pathways play a role in regulating drug metabolism. This article reviewed the impact and single-factor modulating mechanisms of drug metabolism under hypoxia, and put forward the speculation and prospects of multi-factor modulating mechanisms.

Key words: hypoxia; drug-metabolizing enzymes; transporters; modulating mechanism

低氧是指任何原因所致的机体组织细胞得不到充足的氧供，或组织细胞不能很好地利用氧进行代谢活动的病理过程。自 20 世纪 70 年代以来，低氧对机体的影响已经引起了广大研究者的关注，不管是疾病 (如肿瘤、支气管梗阻等) 还是外界环境 (如高原、水下等) 造成的低氧，都会使机体发生一系列生理性变化，甚至是病理性变化，这些变化影响药物在体内的吸收、分布、代谢和排泄 [1–7]。早在 1978 年，Powell 等 [1] 就发现在一些与急性低氧相关的疾病中茶碱的清除率降低 30%~60%，并据此猜测低氧诱导了茶碱清除率的降低，之后 Richer 等的研究证实了该猜测 [2]。Vij 等 [3] 利用模拟低氧环境研究低氧对药物半衰期及疗效的影响，发现乙酰水杨酸、庆大霉素、苯巴比妥和乙酰唑胺的半衰期

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增加，消除速率降低。Gola 等[4]研究显示布洛芬在大鼠体内的平均滞留时间 (mean residence time, MRT) 及半衰期均显著增加。本研究组也利用高原实际低氧环境筛选了大量常用药物，发现在高原低氧条件下机体血氧饱和度显著降低，组织氧气供应失衡，很多药物的药代动力学参数也发生变化[5–7]。高原环境对肝脏代谢能力的影响，导致机体在高原低氧状态下对大部分药物的生物转化率、代谢、及清除率产生影响，从而影响药物的生物利用度。高原低氧环境对不同药物药代动力学参数的影响如表 1 所示，当机体处于高原或模拟高原低氧环境中，药物在体内的清除率降低，半衰期延长，有可能导致毒副作用增强。早期研究表明酶和转运体是药物在体内进行生物转化的主要工具，对药物的代谢参数有显著影响，所以研究低氧状态下的药物代谢必定要涉及酶与转运体。但随着对药物代谢影响因素的深入研究，有研究结果显示，当机体处于病理性状态 (如炎症或低氧等) 时，代谢相关型核受体及细胞因子也会有一定的变化，与药物代谢参数的变化具有相关性[8, 9]。本文将从不同角度综述低氧状态下药物代谢参数的影响因素，并关注药物代谢酶和转运体与核受体及细胞因子之间的相关调控机制。

1 低氧对药物代谢的影响

1.1 低氧对药物代谢酶的影响

药物在生物体内的转化主要包括 I 相反应和 II 相反应两个过程，I 相反应为代谢反应，主要代谢酶包括氧化酶、加氧酶和氧化还原酶，均需要 O_2 参与反应，其中 CYP450 酶是代谢反应的主要酶系，亦最易受到 O_2 浓度的影响，CYP450 酶催化的典型氧化反应可用反应式简单表示：$RH + O_2 + NADPH + H^+ \rightarrow ROH + H_2O + NADP^+$，式中 RH 和 ROH 分别代表药物底物和药物代谢产物，O_2 不足势必会影响酶的催化，因此研究低氧对药物代谢酶的影响是有深刻意义的。CYP450 酶系是一个基因超家族，其中 1~3 家族与药物代谢相关，在人类肝脏中主要有 CYP1A、CYP2A6、CYP2C9、CYP2C19、CYP2D6、CYP2E1 及 CYP3A4，临床中 90% 以上经肝脏代谢的药物是经过这些亚酶代谢的，已有大量研究介绍了低氧状态下 CYP 酶的变化情况 (见表 2)，低氧导致酶的活性或表达降低，减缓药物在体内的代谢，可能增加药物的毒副作用。但是已有报道的研究中，存在实验动物及低氧方式不统一的问题，尤其是高原低氧实验中对急性和慢性低氧没有明确的区分，使得实验结果繁杂，很难得出规律性的结论。本研究组致力于高原低氧对药物代谢影响的研究，建立了高原实地标准实验动物实验室 (4 010 m) 及模拟高原实验室舱，研究中实验对象、低氧方式、实验方法保持统一，后续将进行系统的研究。

II 相反应为结合反应，主要形成能随胆汁和尿液排泄的水溶性代谢物。虽然 II 相代谢酶不直接利用 O_2，但是 O_2 浓度的不足会影响机体内 ATP 的含量，将会间接影响 II 相代谢酶的活性。近几年，不少研究者注意到 II 相代谢酶的重要性，并开始研究低氧对 II 相酶的影响。Li 等[12]将大鼠置于高原实地低氧环境中，*N*- 乙酰基转移酶 2 (*N*-acetyltrans-

表1. 低氧环境下药物代谢参数的变化

Table 1. Effect of hypoxia on pharmacokinetics of drugs

Drugs	MRT	C_{max}	$t_{1/2}$	Ke	AUC	Vd	CL	Major enzymes	Model/hypoxia	References
Theophylline	—	—	—	—	40%↑	21%↓	26%↓	CYP1A2	Rabbit/PaO_2= 55 mmHg	[2]
Acetylsalicylic acid	—	—	25%↑	34%↓	—	—	53%↓	CYP2C19	Rabbit/PaO_2 = 429 mmHg	[3]
Gentamicin	—	—	62%↑	57%↓	—	47%↑	11%↓	CYP3A4	Same as above	[3]
Phenobarbitone	—	—	—	—	—	—	31%↓	CYP2C19	Same as above	[3]
Ibuprofen	—	—	42%↑	—	—	—	—	CYP2C9	SD rat/7 629 m simulated plateau	[4]
Metoclopramide	33%↑	—	—	—	—	—	64%↓	CYP2D6	Wistar rat/Acute exposure to plateau (4 300 m)	[5]
Furosemide	89%↑	68%↑	118%↑	—	110%↑	—	52%↓	CYP2C9	Same as above	[6]
Dexamethasone	8%↑	61%↑	40%↓	—	80%↑	—	44%↓	CYP3A4	Same as above	[7]
Metoprolol	47%↑	—	138%↑	—	—	—	—	CYP2D6	Same as above	[10]
Propranolol	57%↑	353%↑	63%↑	—	443%↑	—	81%↓	CYP2D6	Same as above	[11]

↑: increased; ↓: reduced; MRT: mean residence time; C_{max}: maximum concentration; $t_{1/2}$: half-life time; Ke: elimination rate constant; AUC: area under the concentration-time curve; Vd: apparent volume of distribution; CL: clearance.

表2. 低氧环境下药物代谢酶表达和活性的变化

Table 2. Effect of hypoxia on expression and activity of CYP isoforms

CYP	mRNA levels	Protein expression	Activity	Model	Cause of hypoxia	References
CYP1A		↓	↓	Rat/liver	Acute exposure to plateau (4 300 m)	[12]
	↓	↓		Rabbit/liver	Hypoxia 48 h in 8% O_2	[14]
	↓	↓		Croaker/liver	Oxygen level of water = 1.7 mg/L (normal = 5 mg/L)	[15]
CYP2C	—	—	↑	Rat/liver	Acute exposure to plateau (4 300 m)	[16]
		↑		Bovine retinal endothelial cells	Hypoxia exposure for 6–48 h in 1% O_2	[17]
CYP2E	↓	↓		H-4-II-E cell (rattus hepatoma)	Hypoxia exposure for 24 h in 1% O_2	[18]
	↓	↓	↓	Rabbit, rat/liver	1% O_2/Acute exposure to plateau (4 300 m)	[12, 14]
CYP3A		↓	↓	Rat/liver	Hypoxia exposure for 3 d in 9% O_2	[19]
		↓	↓	Rat/liver	Acute exposure to plateau (4 300 m)	[20]
	↓			Human fetal liver cells	$CoCl_2$-induced hypoxia	[21]

↑: increased; ↓: reduced.

ferase-2, NAT2) 的活性明显降低，特别是在低氧 3 d 后活性的降低达到 38.7%。低氧条件下培养人肺癌细胞，尿苷二磷酸葡萄糖醛酸基转移酶 1A6 (UDP-glucuronosyltransferase 1A6, UGT1A6) 的表达量显著降低 [13]。现有研究对 II 相酶的研究还很不全面，需引起广泛关注。

1.2 低氧对药物转运体的影响

药物透过细胞膜进入体内是药物发挥作用的关键因素，除去药物本身的因素，药物进入细胞膜的跨膜转运机制主要有被动转运、主动转运和膜动转运三种，其中被动转运中的促进扩散和主动转运过程需要转运体的参与。药物转运体主要分为两类，第一类是 ABC 族转运蛋白，又称 ATP 结合盒转运蛋白，这是一个庞大而多样的蛋白超家族，其大部分蛋白的功能是将底物从细胞内外排至细胞外；第二类是 SLC 族转运蛋白，又称可溶性载体，主要功能是转运底物进入细胞，增加细胞内底物浓度。药物转运体一般表达于各种组织的特定细胞膜上，决定药物的吸收、分布和消除以及靶区内药物分布程度。当前对低氧与药物转运体的关系的研究主要集中在肿瘤研究中，因为大多数实体瘤都会使细胞处于微缺氧状态 [22]。Rohwer 等 [23] 总结了不同肿瘤细胞中 P-gp (MDR1) 及多药耐药相关蛋白 (multidrug resistance-associated protein 1, MRP1) 的变化，发现低氧诱导因子调节了这两种转运体的蛋白表达，从而影响化疗药物的疗效。Fradette 等 [14] 的结果显示，家兔在 8% O_2 浓度低氧暴露 48 h 后，肝组织中 P-gp 蛋白相对表达上调 77%。本研究组 [24–26] 也研究了高原实地低氧环境及模拟氧舱环境中大鼠体内转运体的变化情况，结果显示高原实地低氧暴露 72 h 后小肠组织中 P-gp mRNA 与蛋白的相对表达水平分别下调了 50.80% 和 71.30%，说明低氧会导致小肠中 P-gp 的表达下调，使其底物的外排减少，增加其底物在肠道的吸收；模拟海拔 5 000 m 的低压氧舱中持续低氧暴露 24 h 和 72 h 后，与正常对照组相比，低氧组中 6 种药物转运体 (Pept1、Oatp1b1、Oat1、Oct1、Mdr1 和 Mrp2) 的基因表达大多升高，但随着时间的延长，不同组织中的转运体出现不一样的变化趋势。现有的研究大多关注的是肿瘤细胞等非正常细胞的微缺氧状态，而且只考察了低氧对转运体表达量的影响，没有涉及转运能力的变化，在今后的研究中应采取正常组织或细胞低氧处理的方式进行研究，并关注转运体转运能力的变化。

2 低氧对药物代谢酶及转运体的调控机制

2.1 低氧诱导因子1 (hypoxia inducible factor 1, HIF-1)对代谢酶及转运体的调控

HIF-1 是低氧状态下最主要的调节因子，在 HIF-1α 上存在氧依赖性的降解域，在低氧环境中，该降解域不被降解，HIF-1α 稳定表达聚集到细胞核中，与 HIF-1β 结合形成二聚体 HIF-1，HIF-1 与靶基因启动子序列上的低氧反应元件 (hypoxia reactive elements, HREs) 结合，对靶蛋白的转录过程进行调控。低氧状态下，核因子 κB (nuclear factor κB, NF-κB) 通路也能激活 HIF-1 的表达，使 HIF-1 与靶基因启动子上的 HREs 结合增加，转录激活，最终导

致靶基因表达增加。已有大量研究阐明了 HIF-1 对机体药物代谢、能量代谢等代谢通路的影响，在药物代谢通路中，HIF-1 调控的靶基因有代谢酶 CYP2C11、CYP3A6、CYP4B1 以及转运体 GLUT1 和 MDR1 [27]，对药物在体内的代谢和吸收产生了重大影响。

2.2 炎性因子对代谢酶及转运体的调控

低氧会诱导炎症，反过来炎症病灶也会出现局部缺氧。在炎症组织中，低氧也是一个重要的影响因素，是影响组织环境、调节氧依赖性基因的启动者 [28]，应受到高度重视。大鼠暴露于高原实地低氧 3 天，其肝组织病理切片结果显示有明显的肝损伤和炎症，肺泡壁及肺泡细胞充血、水肿，肺组织中 MCP-1、IL-1β、TNF-α 和 IFN-γ 等炎性因子分别增加 51.01%、30.77%、12.64% 和 34.52% (与正常组大鼠相比)，大鼠血清中 activin A、IL-1β、IL-4、IL-10、MCP-1、TIMP-1、TNF-α 均显著升高 [29]。有大量研究表明炎性因子对药物代谢有显著影响，大多数情况下均为负向调节，即减缓代谢，增加体内药物毒性 [30, 31](见表 3)。现有的研究结果显示炎性因子对代谢酶和转运体的调节与 NF-κB 通路密切相关。NF-κB 是免疫应答、炎症反应中具有信号整合作用的转录因子，具有很多生物学功能。炎症因子介导的 NF-κB 通路的激活是通过连续磷酸化、泛素化以及降解其通路抑制元件 IκB 激酶 (inhibitor of κB kinase, IKK) 来调控，而该信号通路对药物代谢酶及转运体的影响可能有三种方式：(1) 直接与基因启动子结合；(2) 抑制药物代谢型核受体；(3) 通过转录后水平调节相关酶与转运体蛋白质的稳定性 [32–34]。

2.3 低氧环境下微小RNA (microRNA, miRNA)对代谢酶及转运体的调控

近年来研究显示在肿瘤细胞的微缺氧环境中，有一些 miRNA (包括 miR-23，-24，-26，-27，-103，-107，-181，-210 和 -213) 被诱导，并且有可能是通过 HIF-1 通路进行调控的 [39]。miRNA 是调控靶基因转录后水平的非编码 RNA 片段，研究显示人类 30% 的编码蛋白基因受其调节 [40]。有越来越多的研究证明 miRNA 可以调控大多数的代谢相关基因。He 等 [41] 综述了大量文献后总结了 miRNA 调节药物代谢的通路图，该通路图中包含了 120 个 miRNA 和 261 个代谢相关基因，miRNA 与药物代谢的关系密切，一方面是 miRNA 可以直接调节代谢酶与转运蛋白基因的 3'UTR 片段；另一方面 miRNA 可以调节与代谢相关的核受体，这为今后研究低氧环境对药物代谢的影响机制提供了新的思路。

3 展望

低氧环境下，影响药物代谢参数的关键因素代谢酶和药物转运体均会发生变化，而研究也显示机体在低氧时 HIF-1、miRNA 及炎性因子也会发生变化。本研究组通过大量文献的研读，发现影响代谢酶与转运体的通路与核受体密切相关。核受体是一组配体依赖性转录因子超家族，它的结构包括配体结合区和高度保守的 DNA 结合区，其中配体结合区可使核受体与异生物质或激素直接结合，DNA 结合区可以结合靶基因的启动子区域。核受体与药物代谢过程中的基因表达调控密切相关，其中代谢型核受体 PXR 和 CAR 调控 CYP1A、CYP2B、CYP2C、CYP3A、UGTS、SULTS、P-gp 等基因的表达 [42]。然而在现有的低氧研究中，核受体对药物代谢的关键作用被忽略。因此，研究核受体对低氧环境下药物代谢的调控作用非常重要。在已有的研究基础上 [29, 43–45]，本研究组提出低氧状态下药物代谢的多因素调控机制 (见图 1)。当机体处于低氧状态时，以药物代谢酶及转运蛋白为主线，HIF-1、炎性因子及核受体均对酶和转运蛋白有一定的调节作用。我们认为药物代谢酶、药物转运蛋白、HIF-1、

表3. 炎性因子对药物代谢酶和转运体的调控

Table 3. Modulation of cytokines on drug-metabolizing enzymes and transporters

Cytokines	Targeted protein	mRNA level/Protein expression/Activity	Model/Hypoxia	References
IFNα-2b	CYP1A2/2C19/2D6	Activity↓	Patients with high-risk melanoma	[30]
TNF-α	CYP2C11	Activity↓	Patients with congestive heart failure	[31]
IL-1β/IL-2	CYP1A2/1A2/3A6	Activity↓/Protein expression↓	Rabbit/Hypoxia 48 h in 8% O_2	[35]
LPS	CYP2C11/3A2/2E1	Activity↓/Protein expression↓	Rat/LPS-induced inflammation	[36]
LPS	P-gp	Activity↑/Protein expression↑	Proximal tubular epithelial cells	[37]
IL-1β/IL-6/IFN-γ	P-gp	Protein expression↑	Caco-2 cell	[38]

↑: increased; ↓: reduced.

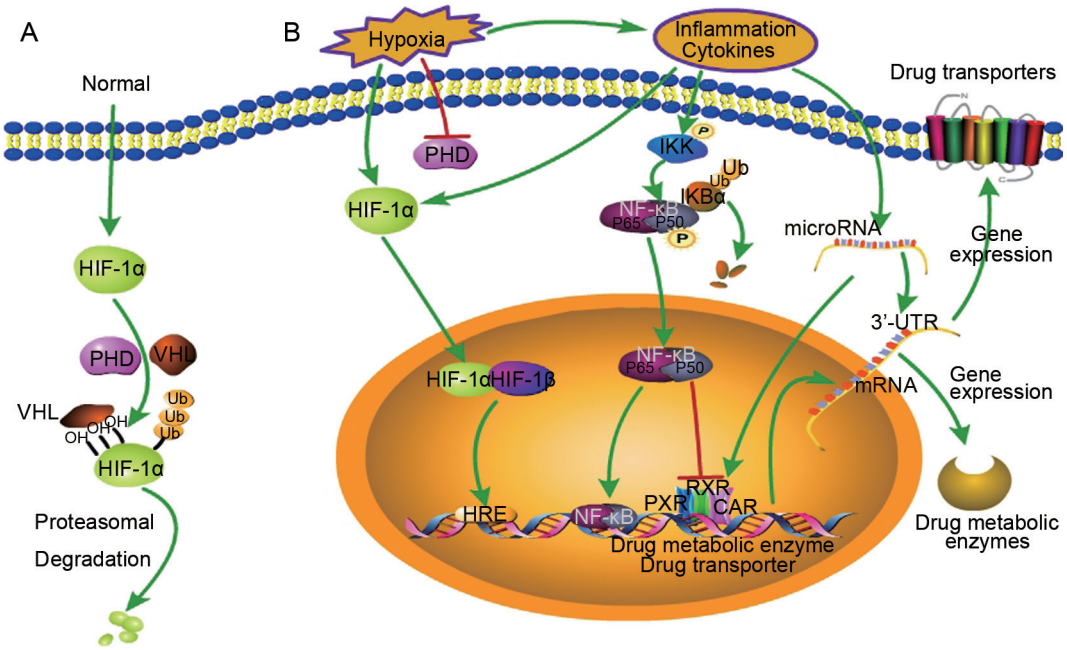

图 1. 低氧对药物代谢影响的多因素调控机制

Fig. 1. Multi-factor modulating mechanism of drug metabolism under hypoxia environment. *A*: The degradation process of HIF-1α in the normal condition. HIF-1α is recognized by the ubiquitin ligase enzymes (Von Hippel-Lindau syndrome, VHL) after prolyl hydroxylase domain (PHD)'s hydroxylation, then it can be ubiquitinated and degraded by proteasomes, and so HIF-1α remains a relatively low level. *B*: Hypoxia induces inflammation and the release of cytokines, then cytokines will influence HIF-1α, NF-κB and microRNA, which can regulate the DNA of nuclear receptor, drug-metabolizing enzymes and transporters, and their expression and structure. Besides, HIF-1α will halt the degradation and stay in organism, because hypoxia inhibits PHD. IKK: inhibitor of κB kinase; PXR: pregnane X receptor; CAR: constitutive androstane receptor; RXR: retinoid X receptor.

炎性因子、核受体之间存在一定的相互作用，其机制应该是多因素相互调节。相关研究正在进行，该多因素调控机制的研究将是低氧环境药物代谢动力学研究的新方向，亦为深入研究低氧环境下药物代谢动力学参数变化提供理论依据，并为研究低氧环境下药物作用新靶点提供思路。

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