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内皮素及其受体与缺血性心脏病

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[摘 要] 内皮素(endothelin，ET)是内皮细胞中分离出的一种活性多肽，是迄今所知最强的缩血管物质之一。它不仅存在于血管内皮细胞中，也广泛存在于心脏、大脑、肺和胃肠道系统中，是调节心血管功能的重要因子，并对缺血性心脏病的发生、发展起非常重要的作用。本文对ET及其相关受体的产生及水平，在心脏缺血性病变如缺血-再灌注损伤(ischemia/reperfusion injury，I/R)、心肌无复流、室性心率失常等中的作用作一综述。

[关键词] 内皮素；缺血-再灌注损伤；心肌无复流；室性心律失常

Endothelin and its receptors and ischaemic heart disease

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Abstract Endothelin is an active polypeptide isolated from endothelial cells and the strongest vasoconstrictor known to date. It not only exists in vascular endothelial cells, but also widely exists in the heart, brain, lung and gastrointestinal system. It is one of the most important factors regulating cardiovascular function, and plays a very important role in the occurrence and development of ischemic heart disease. This article reviews the production and level of endothelin and its related receptors in ischemic heart disease, such as ischemia-reperfusion injury, no-reflow, ventricular arrhythmia and so on, and looks forward to its application prospects.

Keywords endothelin; ischemia-reperfusion injury; myocardial no-reflow; ventricular arrhythmia

世界卫生组织2011年《全球非传染性疾病现状报告》发布的数据显示：全球大约30%的死亡是由心血管疾病引起的，而缺血性心脏病是全世界范围内心脏疾病最主要的死亡原因之一。经皮冠状动脉介入术(percutaneous coronary intervention，PCI)能快速有效地恢复先前缺血区域的血流，可显著降低其病死率和并发症。然而，冠状动脉闭塞的任何时期以及血流恢复灌注后都会对心肌造成损伤，这一重要过程称为缺血-再灌注损伤(ischemia/reperfusion injury，I/R)。心肌I/R对心脏的损伤导致的心功能障碍主要包括致死性再灌注损伤、无复流现象、灌注性心律失常等几种类型[1]。心肌I/R的发病机制主要为血管内皮细胞损伤。血管内皮细胞损伤后释放的内皮素(endothelin，ET)可能对心

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肌I/R的发展具有病理生理学重要性，特异性ET受体拮抗剂的最新发展也为研究和澄清这一问题开辟了新的可能性。然而，其发生机制非常复杂。

1 ET 及其受体的亚型及分布

ET是从培养的猪主动脉内皮细胞中分离纯化出的一种活性多肽[2]。ET的生理和病理生理作用已被广泛研究，是迄今所知最强的缩血管物质，它不仅存在于血管内皮细胞中，也在不同的器官和细胞类型中广泛表达，包括心、大脑、肺和胃肠道系统，是调节心血管功能的最重要因子之一，对于维持血管张力和心血管系统的稳态起非常重要的作用。ET主要有3个亚型：ET-1，ET-2，ET-3。ET-1在心血管系统中是最常见的亚型，在调节冠状动脉张力中起关键作用，对冠状动脉性疾病的预后性有较好的预测价值[3]。ET-1主要由内皮细胞、心内膜和心肌合成并释放[4]。通过静脉或冠状动脉内途径给药，会发现ET-1可引起冠状动脉强烈收缩，这可能会导致心肌缺血。此外，ET-1可显著缩短心肌缺血性挛缩的时间，提示ET-1有直接的促缺血作用。ET-1还被证明在各种离体心脏制剂中发挥正性肌力作用，这可能与ET-1的促心律失常作用有关[5]。

在哺乳动物组织中，ET主要通过2种受体亚型起作用：A型(ETA)与B型(ETB)，这2种受体属于7-跨膜结构域受体家族[6]。ETA和ETB受体均存在于人的心肌和冠状动脉中，但以ETA受体为主。ET1和ET2激活ETA受体的程度相当；然而，ET3并不能激活ETA受体。另一方面，所有ET对ETB受体具有相同的亲和力[7]。在冠状动脉的生理条件下，平滑肌细胞中表达的ETA受体主要介导血管收缩作用，而ETB受体主要存在于内皮细胞中，参与介导血管舒张作用，通过释放NO、前列环素(prostacyclin)和内皮细胞衍化的超极化因子(endothelium-derived hyperpolarizing factor，EDHF)来扩张血管[8-10]。ET-1通常在与ETB受体结合后在细胞内代谢，如在内皮细胞的细胞膜中[11]，而在病理生理条件下，ETB受体也可能在血管平滑肌细胞中表达，介导血管收缩[12]。在大鼠心肌I/R模型中，位于冠状动脉的ETB受体介导的血管收缩反应增强，ETB受体上调可能会使缺血后冠状动脉的血管张力向收缩状态移动，并减弱缺血心肌的血流[13]。

然而，ET受体拮抗剂可减少心肌梗死面积，提高心肌缺血后心肌功能的恢复[14]。在严重I/R期间，ETB和ETA受体的特异性拮抗剂可能对冠状动脉和心肌产生类似的保护作用；在轻度I/R期间，ETB受体的选择性拮抗剂，与ETA受体的相反，可能对保护冠状动脉和心肌缺血无作用[15]。而有研究[16]表明：远程预适应刺激可以激活血管内皮细胞，释放血液中的ET-1，通过联接蛋白43和Akt/GSK-3β信号通路激活心肌ETA和ETB受体，从而触发心肌保护。

2 ET-1 对心肌 I/R 的影响

ET-1释放的来源可能是来自受到缺血后损伤的区域，因为在I/R损伤猪模型的研究中发现冠状动脉左前降支短暂和长期阻塞都可以从心肌受缺血损伤的区域使ET-1溢出增加。ET-1在缺血区的心肌组织水平比非缺血区高出3~7倍，提示ET-1在I/R过程中合成增加[17]。在缺血和再灌注的过程中，有研究者[18]发现大鼠心脏膜中^{125}I标记的ET-1结合位点增加，支持ET在I/R中上调的观点。在急性心肌梗死发作的第1天内或者PCI术后，患者的血浆ET-1水平增加[19-21]，而ST段抬高心肌梗死(ST segment elevation myocardial infarction，STEMI)患者血浆ET-1水平显著高于非STEMI患者[22]。在心肌缺血的动物模型[23]中，也可以发现血浆ET-1水平有所提高。

ET-1升高对心肌再灌注损伤的严重程度或进展有显著影响[24]。ET-1在急性心肌梗死过程中释放，并可能刺激细胞内钙离子浓度的增加，在I/R中诱导心肌细胞凋亡[25]；在大鼠I/R模型中，内源性ET-1和外源性ET-1均能扩大心肌梗死灶面积，这可能与一氧化氮(NO)的生成减少和抗氧化防御机制相关[26]。ET和NO是相互拮抗的血管活性物质，ET在心肌I/R中的作用通过NO生成而增强[27]。上述结果表明ET可能在心肌I/R中起重要作用。

另一方面，外源性ET也被证明能在心脏中产生类似于预处理的效应[28]，而ET-1预处理对新生大鼠心肌细胞缺氧损伤的保护作用也有报道[29]。ET-1信号通路的激活已被证明对慢性间歇性低氧有心脏保护作用[24,30]。远程预处理刺激可激活内皮细胞从而释放血液中的ET-1，通过连接蛋白43和Akt/GSK-3β信号转导途径触发心脏保护[16]。ET-1在远程预处理中的心脏保护作用是通过在远程预处理之前用选择性和非选择性ETA和ETB拮抗剂预处理大鼠来实现的。研究[31]表明：用bonsentan(ET受体阻滞剂)预处理可显著减弱低氧预处理诱导的内皮依赖性舒张功能恢复和心肌I/R。表明远程预

处理可以增加ET-1的释放，ET-1可以通过血液传播到心脏以激活心肌ETA和ETB受体，从而触发心脏保护。

2.1 ETA 受体与心肌 I/R

在正常生理条件下，ETA受体主要存在于血管平滑肌中，具有强烈的血管收缩作用[32]。内源性ET-1在急性I/R心肌细胞凋亡中起作用，ET-1的这种有害特性似乎与ET-A受体亚型的激活有关。ET-1和ET-3诱导冠状动脉血管平滑肌细胞中ETA mRNA表达的下调，但这种下调不影响ETA受体的蛋白质密度或功能性血管收缩反应[33]。ETA受体拮抗剂BQ123具有减少ET-1对兔心肌梗死后细胞凋亡和梗死面积影响的急性细胞保护作用[25,34]。心脏交感神经活性增强及其对神经末梢去甲肾上腺素(noradrenaline，NE)溢出的影响被认为是加重缺血心肌细胞损伤的重要因素，ETA受体拮抗剂ABT-627能抑制交感神经末梢外源性NE释放[35]。有实验[36]通过选择性ETA和非选择性ETA/ETB受体阻滞剂，发现ET系统与NO之间存在密切关系，提示ETA的保护作用是通过提高NO的生物利用度介导的，从而保护内皮功能。

BSF 461314是一种新型、非肽、高选择性的ETA受体拮抗剂，在猪I/R模型[37]冠状动脉结扎后，心肌I/R后ET-1免疫反应性水平升高，而给予BSF 461314后ET-1免疫反应性明显减弱。ETA受体抑制剂对心脏的保护作用可能与抑制中性粒细胞介导的损伤有关。在缺血末期和早期再灌注期间局部应用ETA受体抑制剂LU-135252可减少心肌坏死的程度，这与降低心肌过氧化物酶活性显著相关[38]。

2.2 ETB 受体与心肌 I/R

ETB受体在动脉粥样硬化[39]、心脏缺血[13]、肺动脉高压[40]等心血管疾病中呈上调状态。在人体动脉粥样硬化冠状动脉中，血管平滑肌细胞中ETB受体表达增加[41]，而心肌梗死后患者冠状动脉ETB受体mRNA水平升高[42]。研究[13,43]表明：在心肌I/R后，位于阻塞下游冠状动脉的ETB受体介导的血管收缩反应增强，这种增强反应与血管平滑肌细胞中ETB受体蛋白水平的增加有关，这意味着更多的ETB受体形成，而收缩性ETB受体的上调可以将缺血后冠状动脉中的血管张力转变为收缩状态并且减弱缺血心肌的血流[12]。以上结果表明冠状动脉ETB受体表达的改变可能参与并增强血管张力，从而损害心肌血流。

ETB受体上调可能涉及MEK-ERK1/2信号通路的激活[44]，而在体内使用特定的MEK1/2抑制剂U0126，降低了血管收缩性ETB受体的表达以及心肌I/R后ET-1的表达[45]。研究[46]表明：ETB1/2选择性拮抗剂BQ788在离体心脏对缺血的早期反应和缺血后再灌注中均具有保护作用。

3 ET 与心肌无复流或慢复流

ET对无复流的可能机制：ET-1的血管收缩作用主要作用于小阻力冠状动脉，因此，I/R损伤内皮细胞中ET-1的释放增强，可能导致微血管强烈而持续的收缩[47]。ET-1对多形态核(polymorphous nucleus，PMN)白细胞也有相关作用，这可以解释ET-1与无复流的关系[48]。此外，ET-1能增强微血管通透性，导致微血管水肿[49]。

血管造影显示无复流的患者入院时ET-1血浆水平显著升高[47]。血浆ET-1水平对无复流现象具有预测价值[50]。血浆ET-1水平可独立预测STEAMI患者和2型糖尿病STEAMI患者PCI术后无复流现象的发生[47,51]。激活内皮细胞释放的ET-1有利于无复流。慢复流患者右心房起搏时血浆ET-1水平升高[52]，尼可地尔[N-(2-羟乙基)硝酸烟酰胺]是治疗各种缺血性心脏病的一种有效的血管舒张药[53]，通过上调血浆NO水平和下调ET-1水平，改善胸痛症状和心功能，在冠状动脉慢复流方面呈现出有益的效果[54]。

ET-1拮抗剂可能对无复流的治疗有帮助[47]，在离体心脏制剂中，不同的受体拮抗剂导致心脏收缩和舒张功能、冠状动脉血流、内皮功能的改善，以及无复流面积[55]和缺血性挛缩的减少。ET-1拮抗剂的药物治疗应成为今后研究的主要目标，以减少STEAMI患者的无复流，改善其预后。

4 ET 与室性心律失常

室性心律失常是指起源于心室的心律紊乱，包括室性早搏(室早)、室性心动过速(室速)、心室颤动(室颤)等，急性冠状动脉闭塞刺激交感神经的激活，构成了缺血性室性心律失常的基本机制[56]。当给狗静脉注射ET-1时，会引起心室心动过速[57]。研究[58]表明：ET-1增加I/R后心肌去甲肾上腺素释放，增加了豚鼠心脏室颤的发生率。

在一些动物模型[26]中，ET受体拮抗剂可减少梗死面积，发挥抗心律失常作用。ET-1在冠状动脉闭塞后早期增强了交感神经的激活，这种作用

是由ETA受体介导的[59]。ETB受体在急性心肌梗死过程中调节自主反应，这一调节对心肌梗死后早期室性快速心律失常具有重要意义[60-61]。通过降低ETA介导的交感神经刺激，ETB受体对心肌梗死后I期室性心律失常具有保护作用，而ETB缺乏大鼠则在II期心律失常发生过程中有所下降[62]，但是其机制尚不清楚。心肌拉伸诱导的血管紧张素II的释放激活了ET的释放[63]，而用BQ-123阻断ETA受体，并不能改变室颤或心律失常[64-65]。这些研究结果表明ET-1在室性心率失常发生发展过程中所扮演的复杂角色，以及未来对此问题进行研究的必要性。

5 结语

ET及其受体在缺血性心脏疾病中的作用不容小觑。阻断ET对于缺血性心脏病是有益的，但这种活性肽也具有保护作用。因此，在能够开发出最合适的抗ET疗法之前，仍有诸多问题亟待解决。例如，能否阻断ET-1对心肌细胞的有害性方面？关于ET导致微血管强烈收缩和促心律失常的作用，是否能够解决围绕ET-1直接作用与间接作用的争论？未来仍需进一步对ET及其受体进行研究，揭示ET在心血管疾病中的作用，为治疗缺血性心脏病奠定基础。

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