

文章编号 :1004-0374(2011)01-0057-06

心脏交感神经和心肌间质重塑的共同通路——蛋白激酶 C 途径

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摘要: 心脏交感神经和心肌间质对维持正常心功能有重要作用。心血管患病时, 两者均发生不同程度的重塑, 并互相影响, 这些变化对疾病进展发挥重要影响。研究证据显示, 两者间的相互作用可能通过蛋白激酶 C 介导, 对交感神经功能异常和心肌纤维化都发挥重要作用。

关键词: 蛋白激酶 C; 交感神经; 心肌间质

中图分类号: Q555.7; R322.85; R540.5

文献标识码: A

Protein kinase C pathway on cardiac sympathetic nerve neuroplasticity and myocardial interstitial remodeling

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Abstracts: Cardiac sympathetic nerve and myocardial interstitium play important roles for preservation of heart function. Different extent of the interstitial remodeling and neuroplasticity commonly occur in many kinds of cardiovascular diseases. The abnormalities interact and contribute to progression and worsening of the diseases. There is accumulating evidence suggesting that protein kinase C activation as a regulator involves in and mediates interaction between the neuroplasticity and remodeling under such conditions, which plays a critical role in the nerve dysfunction and myocardial fibrosis.

Key words: protein kinase C; sympathetic nerve; myocardial interstitium

近年来, 心血管研究领域的科技人员更加意识到, 并且更为关注不同心脏组织间互相影响及其作用的重要性。心脏交感神经(sympathetic nerve)和心肌间质(myocardial interstitium)对维持正常心功能均有重要作用。心脏交感神经由颈、上胸部脊柱旁心脏交感神经节发出的节后神经纤维沿大血管到达心底, 通过心外膜神经丛(epicardial nerve plexus)分布于心脏各部分, 通过释放神经递质——去甲肾上腺素(norepinephrine, NE)和再摄取(reuptake)NE 调控心脏变时(chronotropic)、变力(inotropic)及传导(dromotropic)等功能; 心肌间质, 即细胞外基质(extracellular matrix, ECM)主要由以 I、III 型胶原(分别占 ECM 的 80%、10%)为主的胶原纤维构成,

发挥维持心脏正常形态和功能作用^[1-3]。许多心血管疾病, 特别是心力衰竭(heart failure, HF)时, 常发生不同程度的交感神经、心肌间质异常。众所周知, 两者异常变化对心血管疾病的进展及其预后发挥重要影响^[4-9]。越来越多的研究证据提示, HF 时两者变化可互为影响, 确切机制目前仍不完全清

收稿日期: 2010-06-10; 修回日期: 2010-07-12

基金项目: 天津市科委自然科学基金重点课题(09JCZDJC19500); 国家自然科学基金项目(30740010, 30871072); 武警医学院科研基金重点课题(WKH 2008Z04)

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楚^[10-13]。目前研究表明,蛋白激酶(protein kinase C, PKC)激活可能是介导两者间相互影响的重要因素之一^[14-16]。阐明这些复杂的互相影响机制,可为进一步认识心脏交感神经、心肌间质重塑的相关因素、疾病的进展机制和寻求有效的治疗方法奠定基础。

1 心血管患病时交感神经变化及其意义

多种心血管疾病,特别是发生HF时均发生心脏交感神经变化,包括神经支配密度和神经再摄取(reuptake)功能改变。交感神经异常的主要特征为(1)心脏中NE含量减少,即交感去神经(sympathetic denervation);(2)交感神经激活,循环NE水平明显增高;(3)血浆NE增高水平与HF患者预后呈负相关,NE显著增高的患者预后不良^[2,7-9]。根据组织学和神经功能研究结果,心血管疾病中交感神经异常大体可分为有交感神经密度改变,包括神经密度降低-交感去神经、神经密度增加;以及无神经密度变化,仅表现为再摄取NE功能减退的功能性交感去神经(functional denervation)两类^[17-23]。

临床和实验研究观察到,心血管疾病,如高血压、心肌病、冠心病心肌缺血、心肌梗死(myocardial infarction, MI)、不同病因的HF,以及代谢性疾病糖尿病、神经系统疾病帕金森病和老龄过程等,均可出现心脏交感神经变化(neuroplasticity),包括神经密度降低、不均匀分布(heterogeneous innervation)、神经再生(regeneration)及神经再摄取功能(即再摄取1, reuptake 1)异常等,这些变化常同时存在。无论是否同时存在神经密度变化,甚至神经密度增加,均可出现神经摄取功能降低^[24-31]。然而,交感神经密度降低也非一定同时伴有神经再摄取功能下降^[32],可能说明摄取功能有较强的储备。交感神经密度与神经递质NE再摄取转运蛋白密度并非一定呈一致性变化。组织学研究观察到,心房交感神经密度相对高于心室,然而左心室NE再摄取转运蛋白密度却最高^[33,34]。

交感神经再摄取功能是通过存在于神经突触前膜上的微量去甲肾上腺素转运蛋白(norepinephrine transporter, NET)实现的,通过NET可使高达90%释放的NE回收至突触前膜内,从而调控交感神经信号传递^[21,35]。若摄取功能下降,可使释放后的NE在心肌间质中积累,浓度增加,产生NE信号放大作用。长期NE刺激最终可致心肌对肾上腺素能刺激收缩力增加反应钝化(blunted)、 β -肾上腺素能受

体(β -adrenergic receptor, β -AR)密度/功能异常、去敏感(desensitization)、心肌肥厚、心肌细胞坏死/凋亡、心律失常,甚至心性猝死^[8,9,23]。因此,交感去神经及再摄取功能异常可导致严重的不良结局,促进疾病恶化、进展。

虽然交感神经异常在心血管病中发挥重要作用,并一直受到广泛关注,特别是疾病过程中心脏交感神经重塑调控机制、神经功能异常机制及如何改善等问题,但近年来相关研究并无重大进展。最近较为重要的研究结果是,Münch等^[36]观察到直接心肌注射表达NET质粒补充外源性NET,过表达NET可提高模型大鼠心脏交感神经NE再摄取,并改善心功能;靶组织产生的神经生长因子(nerve growth factor, NGF)主要通过与其受体TrkA结合,以轴突转运方式进入神经元,发挥生物学作用。Kreusser等^[37]报道,通过开胸一次性神经节直接注射的方法补充外源性NGF,32h后心脏NE摄取提高、心功能改善,心脏交感神经密度、NET mRNA表达无明显变化,推测可能由于使内化(internalization)的NET重新膜表达,而产生上述效果。然而,用开胸注射给药方法改善心脏神经摄取功能,其临床应用显然并非简单易行。因此,应寻找其他更为简单有效的治疗方法。我们最近采用心脏神经节周围颈部肌肉注射的方法,给主动脉狭窄2月大鼠补充外源性NGF(连续5d),观察到左心室NGF表达显著增高,左心室重塑明显减轻,左心室收缩功能有所改善,同时心脏交感神经节NET mRNA表达和左心室交感神经密度无明显变化(待发表)。

2 不同心脏负荷对心肌间质变化和交感神经重塑的影响

交感神经与心肌间质两者变化存在互相影响的关系,交感神经异常可影响心肌间质^[10-13]。Briest等^[10]实验观察到,NE对心肌间质胶原重塑发挥重要影响,持续静滴NE增加大鼠心肌I/III型胶原表达、胶原含量增加。Perlini等^[11]观察不同抑制交感神经方法对压力超负荷(pressure overload, POL)后心肌间质纤维化的影响。结果显示,药物(6-羟基多巴胺, 6-hydroxydopamine)交感去神经、 α -肾上腺素能受体阻滞剂(多沙唑嗪, doxazosin)均有抗心肌纤维化作用(antifibrotic effect),可使自发性高血压大鼠心肌胶原含量显著降低,并且两者均影响基质金属蛋白酶2(matrix metalloproteinase 2, MMP-

2)和组织型 MMPs 抑制物-2(tissue inhibitors of metalloproteinases 2, TIMP-2)活性,可使 TIMP-2/MMP-2 比值降低;β-肾上腺素能受体阻滞剂(普萘洛尔, propranolol)对胶原含量无明显影响,使 TIMP-2/MMP-2 比值增加。这些证据说明交感神经异常与心肌间质重塑间有密切关系。

另一方面,心肌间质改变也影响心脏交感神经支配。动物 MI 后 MI 远离区交感神经密度明显高于 MI 周围区密度。El-Helou 等^[12]观察到,与对照组比较,糖皮质激素(地塞米松)干预可使 MI 后非 MI 区心肌胶原(collagen α_1 type 3)mRNA 显著降低,同时心肌交感神经密度、生长相关蛋白 43(growth associated protein 43, GAP43)、NGF mRNA 及蛋白表达均下降。

不同类型的心脏负荷导致不同特征的心肌细胞、心肌间质重塑,例如 POL 导致显著心肌纤维化, I/III 型胶原表达、胶原含量增加,而容量超负荷(volume overload, VOL)相反,心肌胶原含量下降^[38,39]。同时,心脏超负荷状态交感神经密度、摄取功能变化也不同。POL 后心脏交感神经密度增加或保持不变,Backs 等^[40]观察到主动脉缩窄大鼠心脏交感神经密度无明显变化,但 NET 再摄取功能/结合位点数量下降。Nyquist-Battie 等^[41]报道,相同模型早期左心室交感神经密度、心肌 NGF 蛋白水平无明显变化,缩窄后 1 周尽管 NGF 蛋白显著增高,但 NE 再摄取结合位点数量显著减少。与此相近,肺动脉高压导致右心室压力超负荷,大鼠右心室心肌 NGF mRNA 表达水平和交感神经密度均显著增加,NE 再摄取下降^[42]。另外,抑制心肌纤维化药物(螺内酯, Spironolactone)可改善盐敏感高血压 Dahl 大鼠(saltsensitive Dahl rats, DS)心脏 NE 再摄取及心肌 NET 位点密度,控制血浆 ET-1、NE 水平,同时显著提高生存率和心功能^[43]。

与此相反,动静脉瘘致容量超负荷(volume overload, VOL)大鼠左心室交感神经密度降低,但 NET 摄取功能、NGF mRNA 表达均无降低^[32], Somsen 等^[44]观察到兔双负荷 HF 模型左心室交感神经 NE 再摄取无下降。上述证据说明,交感神经密度、再摄取功能变化与心肌间质胶原含量变化呈相反关系。

另外,心脏肾素-血管紧张素-醛固酮系统(renin-angiotensin-aldosterone system, RAAS)也与 HF 时心脏交感神经异常关系密切。Kawai 等^[45]观察到右心室双负荷(肺动脉缩窄加三尖瓣撕裂)导致右心

衰(right heart failure, RHF)的犬,其右心室交感神经密度减少,且心肌摄取^[3H] NE 能力和 β-AR 密度降低。血管紧张素转化酶抑制剂(angiotensin-converting enzyme inhibitors, ACEI)治疗可使这些异常变化基本恢复至对照组水平。

兔心脏快速起搏致 HF 模型起搏后 1、2 周,心脏交感神经、左心室 β-AR 密度无变化,4~8 周两者密度显著下降,停止起搏后迅速恢复至对照组水平^[46]。ACEI、血管紧张素 AT₁ 受体阻断剂(angiotensin AT₁ receptor blocker, ARB)均可使快速起搏 HF 模型心脏交感神经再摄取异常得到显著恢复,两者联合时作用加强^[46-48]。ACEI、ARB、β-ARB、醛固酮抑制剂治疗 HF 的临床试验也显示交感神经功能改善^[49,50],说明心脏 RAAS 激活对 HF 时交感神经异常发挥重要影响。此外,RAAS 对心肌间质重塑的影响也是众所周知的^[51]。

3 蛋白激酶信号途径改变对心肌间质变化与交感神经/NET 的影响

NET 内化可能是心脏交感神经再摄取功能下降的原因之一^[34]。研究显示,蛋白激酶 C(PKC)激活与 NET 内化有关,可降低转染 NET 的 HEK-293、LLC-PK1、COS-7 细胞 NE 摄取能力、表面表达,但以何种 PKC 亚型的作用为主目前尚不清楚^[21,23,52]。PKC 主要存在于细胞核内,对细胞增殖、分化、转化、凋亡信号转导发挥重要作用,与心血管疾病关系密切。PKC 属于磷脂-依赖丝氨酸/苏氨酸激酶(phospholipid-dependent serine/threonine kinases)家族,哺乳动物 PKC 有 13 亚型,包括通过 Ca²⁺/二酰基甘油(diacylglycerol)途径激活的传统亚型(conventional PKCs, cPKCs)α、βI、βII、γ;仅通过二酰基甘油途径激活的新亚型(novel PKCs, nPKCs)δ、ε、η、θ;不依赖此途径的非典型亚型(atypical PKCs, aPKCs)ζ、ι/λ,以及通过 G 蛋白依赖异构调节模式(G-protein dependent allosteric mode)的 PKN 亚家族(PKN1、PKN2 和 PKN3)^[14,53]。心脏成纤维细胞(myocardial fibroblast)是重要的心脏细胞成分,是间质纤维蛋白和间质中多种蛋白酶的主要来源,对 EM 发挥重要影响^[1,6,51,54]。心脏超负荷(包括 POL、VOL)影响成纤维细胞活性。心脏成纤维细胞有 α-、β I-、β II-、ε-、δ-、ζ-PKC 等 6 种亚型,其中 δ、ζ-PKC 亚型与心脏成纤维细胞增生有关^[16]。此外,牵拉心肌成纤维细胞还增加内皮素-1(endothelin-1, ET-1)表达,ET 对 NET 内

化也发挥重要影响^[51,55]。梁栋等^[21]、刘旭东等^[22]，以及Zahniser和Doolen^[35]对PKC激活介导NET内化作用及机制有详细的介绍，在此不再赘述。

Husse等^[15]证明，机械性牵拉可诱导心肌成纤维细胞I、III胶原表达量增加，这种表达变化通过PKC、酪氨酸激酶(tyrosine kinase, TK)信号途径介导，抑制PKC、TK可显著降低胶原表达。而交感神经NET内化也通过PKC途径介导，PKC信号途径激活胶原表达增加、NET内化；相反，抑制这一信号通路则胶原表达减少、内化减轻^[15,52]。提示PKC信号途径对两者发挥反向调节作用，可能是心肌胶原表达增加与NET发生内化间存在的共同信号通路，抑制这一信号通路可能减轻心肌间质纤维化，同时提高NET膜表达，改善神经再摄取功能。

根据上述研究结果，我们推测不同心脏超负荷导致不同心肌间质变化与交感神经重塑/功能变化有共同的信号转导通路，对两者间的互相影响发挥重要作用，这一信号通路激活或抑制可能对此时心肌间质改变和心脏交感神经重塑/功能异常有重要意义(图1)。

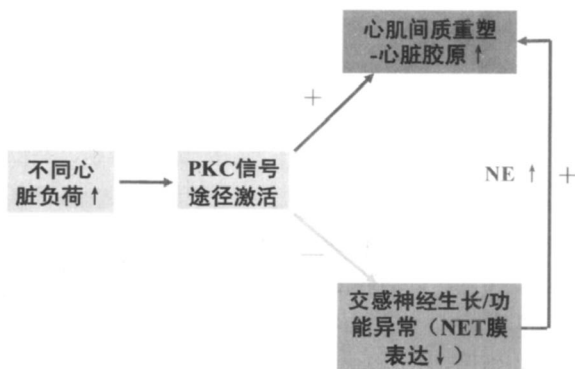


图1 PKC信号途径与心脏交感神经、心肌重塑的关系

注：↑：升高；↓：下降；+：增强；-：减弱

4 结语

交感神经功能和心肌间质异常对多种心血管病和心功能异常发挥重要作用，特别是对HF的发生、进展、预后均有重要影响，并且两者的变化互相影响，PKC激活可能介导其间的相互作用。近年来，尽管对交感神经功能和心肌间质异常的研究逐步深入，仍然有许多问题有待进一步研究，需要阐明其相互作用机制，以修复或减轻两者作为干预靶点可能会成为一种新的心血管病治疗策略。

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