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评 述 多细胞器之间的离子稳态调控专题

β肾上腺素受体对心肌细胞钙信号的调控

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摘要 心脏是血液循环的动力器官. 心肌细胞通过钙致钙释放的机制实现兴奋收缩耦联, 控制着心脏有节律的收缩和舒张. 交感神经递质通过β肾上腺素受体(β-adrenergic receptor, βAR)调控心肌细胞钙信号转导和心脏收缩舒张功能. 在病理条件下, βAR的信号转导和钙信号出现异常, 导致心律失常、心力衰竭、缺血再灌注损伤等心脏疾病的发生. 因此, 阐明βAR信号通路对心肌细胞钙信号的调节对认识心脏疾病的机理和药物研发具有重要意义.

关键词 心肌细胞, β肾上腺素受体, 钙信号转导

心脏通过有节律的收缩和舒张保证全身血液循环正常进行, 是维持机体正常生命活动最重要的器官之一. 交感神经通过释放去甲肾上腺素(norepinephrine, NE)和肾上腺素(epinephrine, Epi)作用于心肌细胞上的肾上腺素受体调控心脏收缩和舒张功能[1]. 但是, β肾上腺素受体(β-adrenergic receptor, βAR)信号通路持续激活则可能会影响心肌细胞的正常钙信号转导, 引发心脏的结构与功能异常, 导致心脏疾病的发生[1,2]. 本文将结合该领域的最新进展分析心肌细胞钙信号及βAR通路对其调控的分子机制和病理变化.

1 心肌细胞钙信号

1.1 心肌细胞钙信号调控的结构基础

成年哺乳动物的心脏由多种类型的细胞组成, 含量最丰富的是心肌细胞、成纤维细胞、内皮细胞以及血管周围细胞. 其中心肌细胞占哺乳心脏总细胞数的30%~40%[3~8], 占心脏总体积的70%~85%[8~12]. 非肌细胞中内皮细胞占比约60%, 造血细胞占5%~10%, 成纤维细胞占据比例低于20%[13]. 尽管非肌细胞占心脏总体积比例相对较小, 但能够提供心肌细胞收缩和长期存活所需的细胞外基质、细胞间通讯以及血液供应[8].

心肌细胞通过一些特化的结构实现其收缩功能. 心肌细胞膜在Z线处向细胞内部凹陷形成复杂的管状网络结构, 即横管(transversal tubule, TT). 光学成像测得的横管平均直径为200~400 nm[14].

同时, 心肌细胞还有一种特化的滑面内质网, 即肌质网(sarcoplasmic reticulum, SR). 肌质网是心肌细胞的钙库. 肌质网由自由型肌质网(free sarcoplasmic reticulum, fSR)与连接型肌质网(junctional sarcoplasmic reticulum, jSR)两种成分构成[15]. fSR相互连接, 主要沿细胞纵向排列, 又称纵行肌质网(longitudinal sarcoplas-

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mic reticulum)[16]. fSR上分布着大量的肌质网钙泵(sarcoplasmic endoplasmic reticulum calcium ATPase 2a, SERCA2a)以及其内源性抑制蛋白受磷蛋白(phospholamban, PLB)[17], 调控钙离子由细胞质向肌质网的回收过程[15,18,19]. jSR膨大成泡状结构, 管腔宽度约为30 nm[16], 与细胞表面膜或横管膜相距仅10~20 nm. jSR膜上分布着雷诺丁受体(ryanodine receptor 2, RyR2). RyR2通过狭窄的间隙与横管或细胞膜上的L型钙离子通道(L-type calcium channel, LCC)耦联. jSR管腔内分布着肌集钙蛋白(calsequestrin 2, CSQ2或CASQ2)[20]. CSQ2是一种低亲和力、高容量的钙缓冲蛋白. CSQ2通过两种跨jSR膜并嵌入jSR管腔的蛋白Triadin和Juntcin与RyR2互作, 对RyR2的钙释放活动进行调控[14,21].

心肌细胞中横管与jSR相互交织形成二联体结构(diad), 又被称为耦联子(couplon), 是心肌细胞兴奋-收缩耦联(excitation-contraction coupling, ECC)的结构基础[22,23]. 在心肌细胞耦联子结构中, 横管与肌质网相距约12 nm[16], 二者之间通过连接蛋白(junctophilin-2, JPH2)相连接. JPH2蛋白的碳端锚定在jSR上, 氮端则结合在横管膜上, 对于维持二联体结构稳定发挥着重要作用. JPH2的敲除会导致胚胎期小鼠心肌细胞中耦联子结构瓦解, 并使得心肌细胞钙瞬变发生异常变化[24].

1.2　心肌细胞钙致钙释放

钙离子是细胞内具有广泛作用的第二信使, 在调节心肌细胞电活动以及收缩功能中发挥着重要作用.

当心肌细胞去极化产生动作电位时, 位于心肌细胞膜或横管上的LCC被激活, 细胞外少量钙离子经此通道流至胞质, 产生内向的钙离子电流, 并激活位于jSR上的RyR2, 使得RyR2通道开放, 肌质网内的大量钙离子流向胞质, 胞质内游离的钙离子浓度可由100 nmol/L迅速升高至1 μmol/L, 这一过程称为钙致钙释放(calcium-induced calcium release, CICR)[25~28](图1). 这一过程中, 可以观察到细胞内不同形式的钙信号. 单个LCC通道开放会引起少量胞外钙离子内流, 使得细胞某一部位钙离子浓度升高, 我们将其称为钙火星(calcium sparklet). 我们证明一个钙火星可激活4~6个RyR2通道开放[29], 引起胞内局部钙离子浓度瞬间升高, 即产生钙火花(calcium spark)[30]. 钙火花既可自发产生, 也可被LCC开放产生的钙电流所激活[28]. 相同时间大量钙火花整合可最终引发心肌细胞整体的钙瞬变(calcium transient), 驱动心肌细胞收缩. 在病理条件下, 钙火花通过钙致钙释放激活邻近区域的RyR2, 形成在细胞内传播的钙波(calcium wave)[28,31~33].

RyR2开放后释放大量钙离子至细胞质, 胞质内高浓度的游离钙离子与附着在原肌球蛋白丝和细肌丝上的肌钙蛋白C (troponin C, TnC)结合, 引发原肌球蛋白丝位移, 解除了粗肌丝肌球蛋白的横桥与细肌丝结合的位阻, 粗肌丝与细肌丝发生相对滑行, 启动心肌细胞收缩[34]. 这一由肌细胞动作电位引发细胞质内钙离子浓度升高并导致细胞收缩的过程被称为兴奋-收缩耦联[25]. 随着RyR2钙释放的终止, 心肌细胞胞质内的钙离子通过SERCA被重新转运至肌质网内存储或通过心肌细胞膜上的钠钙交换体(sodium/calcium exchanger, NCX)等运送至细胞外(图1), 从而使心肌细胞胞质内游离钙离子的浓度逐渐恢复至静息水平, 心肌细胞舒张[19,25,35,36].

2　β肾上腺素受体对心肌细胞的调节

2.1　支配心脏的神经系统

心脏的自主神经系统由心交感神经及副交感神经组成, 二者相反相成, 共同调控心脏功能[37].

心交感神经纤维由起源于脊髓的节前神经纤维与起源于星状神经节的节后神经纤维组成. 节后交感神经纤维的分支延伸至心脏大部分区域, 包括窦房结、心房、房室结、希氏束、蒲氏纤维以及心室肌[38~43]. 交感神经末梢分泌交感神经递质, 主要是NE, 也有部分Epi, 能够提高心率、加快传导、增强收缩力[37,44].

心副交感神经纤维起源于延髓背侧运动核延伸出的迷走神经[38,39], 主要分布于心房, 在心内神经节与节后神经元形成突触[45~49]. 心副交感神经节后纤维释放乙酰胆碱(acetylcholine, ACh), 通过激活毒蕈碱受体(muscarinic receptor), 抑制交感神经系统的活动, 并直接作用于窦房结和心房肌细胞, 降低心率, 减弱心房收缩力[48,50,51].

2.2　心肌细胞肾上腺素受体的表达

NE和Epi引起的生理反应是通过肾上腺素受体(adrenergic receptors或adrenoceptors, AR)介导的[52]. 肾

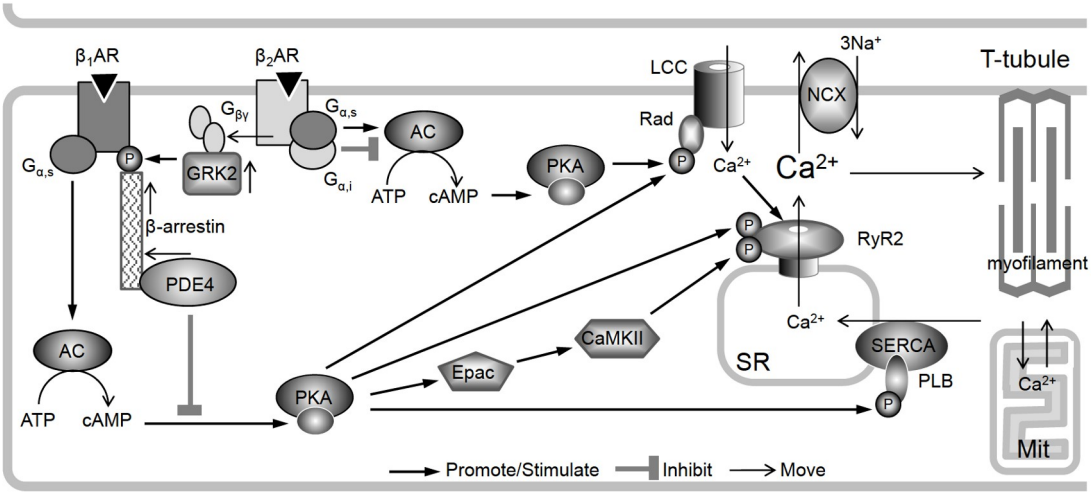

图 1 β肾上腺素受体对心肌细胞钙信号的调控
Figure 1 β-adrenergic receptor regulation of Ca^{2+} signaling in ventricular cardiomyocytes

上腺素受体属于七次跨膜的G蛋白耦联受体(G-protein-coupled receptor, GPCR)家族, 分为α_1、α_2、β_1、β_2和β_3亚型[53,54]. 其中Epi能够激活所有αAR和βAR, 而NE则主要激活αAR和β_1AR[52].

α_1AR主要存在于血管平滑肌, 在心肌中表达较少. α_1AR与G_q蛋白相耦联, 通过激活磷脂酶C等, 调控外周动脉、静脉以及冠状动脉血管平滑肌收缩、左心室收缩[52,55]. α_2AR主要存在于中枢神经系统, 与抑制性G蛋白G_i耦联, 抑制腺苷酸环化酶(adenylyl cyclase, AC), 减少环磷酸腺苷(cyclic adenosine-3′,5′-mconophosphate, cAMP)的产生[56]和磷酸激酶A(phospholipase A, PKA)对下游蛋白的磷酸化[52].

βAR在心肌、血管平滑肌以及脂肪组织中表达较高[52,57]. 在心脏中, β_1AR表达量最多, 占全部βAR表达量的75%~80%, β_2AR占20%~25%, β_3AR则只占极少比例[48,52,58,59]. β_1AR分布于心肌细胞膜或横管膜, β_2AR主要分布在横管, β_3AR也被证实在横管处有分布[60,61].

心肌细胞中β_1AR被Epi或NE激活时, 会启动下游的G_s信号转导通路, 使得G_s蛋白复合体解离为$G_s\alpha$和Gβγ亚基, $G_s\alpha$激活AC, AC催化ATP水解生成cAMP, cAMP作为第二信使又与PKA的调节亚基结合, 使其与PKA的催化亚基分离. 在心室肌细胞中, PKA催化亚基活化后能够对LCC、RyR2、PLB以及肌钙蛋白I (troponin I, TnI)与肌钙蛋白C (troponin C, TnC)等钙信号通路相关蛋白进行磷酸化修饰, 最终使得心肌细胞钙瞬变幅度增加、收缩力增强[62,63]. 在起搏器细胞中, PKA介导的钙信号通路相关蛋白的磷酸化能够增加钙循环以及起搏率[64]. 此外, 有研究指出β_1AR信号通路还能够激活钙/钙调蛋白依赖性蛋白激酶(calcium/calmodulin dependent protein kinase II, CaMKII), 对RyR2、PLB等蛋白进行磷酸化修饰[65](图1).

β_2AR对Epi的亲和力强于NE, β_2AR被激活时, 会启动G_s及G_i两条信号转导通路, 对心脏收缩功能进行调节[66~68]. 即β_2AR被激活时, 通过启动G_s信号通路生成cAMP激活PKA, PKA又能磷酸化β_2AR, 使其与G_i耦联, 抑制AC, 减少cAMP的生成(图1)[69]. 由于β_2AR激活产生的cAMP仅局限在细胞膜或横管膜附近, 仅能对LCC等进行磷酸化, 而不能够磷酸化RyR2以及PLB等钙信号通路相关蛋白(图1), 因而其激活不能增强心肌细胞的收缩能力[63,70,71].

2.3 βAR信号通路对LCC的调控

LCC分为$Ca_V1.1$、$Ca_V1.2$、$Ca_V1.3$和$Ca_V1.4$亚型[72,73]. 在心脏中, 心房肌、窦房结以及房室结中$Ca_V1.2$与$Ca_V1.3$都有所表达, 心室肌细胞则主要表达$Ca_V1.2$亚型[27,74]. $Ca_V1.2$由α_{1C}、$\alpha_2\delta$和β亚基构成. α_{1C}亚基构成$Ca_V1.2$的钙离子选择性孔道, 由四个跨膜结构域(I~IV)组成, 每个结构域包含6个跨膜片段(S1~S6)以及一个在片段5和6之间形成孔的P环, 其中第4个跨膜片段(S4)带正电荷, 是$Ca_V1.2$的电压门控, α_{1C}亚基还

是某些调节蛋白或药物的结合位点. $\alpha_2\delta$和β经非共价键与α_{1C}相连接[75,76]. β亚基与α_{1C}的结合曾被认为对$Ca_V1.2$蛋白在心肌细胞膜的运输起关键作用, 但近期使用β亚基突变小鼠的研究发现, β亚基与α_{1C}的结合并非$Ca_V1.2$蛋白运输所必需的, 但对βAR-PKA刺激引发钙电流增加和心脏收缩增强却是必不可少的[77]. βAR激动所激活的PKA介导$Ca_V1.2$通道钙流入的增加, α_{1C}亚基Ser^{1928}和Ser^{1700}位点以及β亚基Ser^{459}、Ser^{478}与Ser^{479}位点均会受到PKA的磷酸化调控[78~80], 但有研究者认为这些位点的磷酸化并不能解释βAR激活后的$Ca_V1.2$调控[81~85]. 近年来, 相关研究探索了Epi能激动引起心肌细胞钙流入和心肌收缩增强的机制, 指出$Ca_V1.2$通道抑制蛋白Rad介导了这一过程. Rad蛋白具有4个保守的PKA磷酸化位点[86], PKA磷酸化Rad, 降低了其与$Ca_V1.2$ β亚基的亲和力, 进而消除了其对$Ca_V1.2$的抑制作用, 增加了$Ca_V1.2$钙内流[86~89].

2.4　βAR信号通路对RyR2的调控

RyR是迄今为止发现的分子量最大的离子通道, 哺乳动物心肌细胞中主要表达RyR2亚型. RyR2由4个分子量565 kD的同源单体构成四聚体, 每一单体与一个分子量12 kD的FK506-结合蛋白(FK506 binding protein 12.6, FKBP12.6)相连, 总分子量超过2000 kD. RyR2蛋白的胞质结构域包含80%氨基酸残基, 与PKA、CaMKII、蛋白磷酸酶1 (protein phosphatase 1, PP1)、蛋白磷酸酶2a (protein phosphatase 2a, PP2a)等形成复合体, 同多种离子及蛋白质发生相互作用[90~92]. RyR2的活动受到其与FKBP12.6的结合与解离状态以及磷酸化、去磷酸化的调控. FKBP12.6与RyR2的解离能够显著改变RyR2通道的生物物理特性并提高其对钙离子的敏感性[93]. 目前已经证实RyR2上存在多个磷酸化位点能够被β_1AR信号通路所调控, 如人类及啮齿类动物Ser^{2808}或兔Ser^{2809}位点[94]以及Ser^{2030}位点[95]能够被PKA磷酸化, 人类及啮齿类动物Ser^{2814}位点或兔Ser^{2815}位点则能够被CaMKII磷酸化[96]. PKA对RyR2 Ser^{2808}位点的磷酸化调控可能会使得RyR2与FKBP12.6解离, 对钙离子敏感度升高, 通道开放率增加, 钙释放增强[97,98]. 我们的研究证明β_1AR激动使得单个LCC触发RyR2钙释放形成钙火花的成功率及速率提高, 钙火花的幅度增大[99].

2.5　βAR信号通路对PLB的调控

在心肌细胞中, 表达在肌质网上的SERCA2a控制着胞质中钙离子的清除, 在收缩结束时, SERCA2a通过水解ATP将钙离子泵回至肌质网内, 这一过程受到了PLB的抑制性调控[100,101]. PLB是肌质网上的一种单次跨膜的膜蛋白, 由52个氨基酸构成, 其中第1~30位氨基酸位于胞质中, 第31~52位氨基酸位于跨膜区段[102]. 依据功能的不同, 又可将其结构分为一个由Ia结构域与Loop构成的调节结构域, 以及一个由Ib结构域与II结构域构成的抑制结构域. PLB分子以单体及多聚体形式存在. PLB通过与SERCA2a的跨膜结构域结合影响SERCA2a的构象变化进而调控SERCA2a对钙离子的亲和性[103,104]. 当β_1AR信号通路激活时, 活化的PKA和CaMKII分别磷酸化PLB的Ser^{16}与Thr^{17}磷酸化位点, 导致PLB发生构象变化并与SERCA2a解离, 解除了其对SERCA2a的抑制, 导致SERCA2a对胞浆中钙离子回收加快, 并使得心肌舒张速率加快[103,105].

3　影响βAR信号转导的重要分子

3.1　GRK

βAR信号通路的失活受到相关蛋白的精细调控. 当特异性激动剂与βAR受体结合后, G蛋白耦联受体激酶(GPCR kinase, GRK)能够对βAR膜内碳末端结构域的磷酸化位点进行磷酸化调控, 使得βAR与G蛋白的结合能力减弱, 而与抑制蛋白β-arrestin结合能力增强, 抑制βAR信号通路激活, 导致cAMP信号产生量减少; 此外, β-arrestin还能够招募磷酸二酯酶4(phosphodiesterase 4, PDE4), 降解cAMP, 进一步减少cAMP信号对下游信号分子的影响[106]. 因此, GRK以及β-arrestin的作用使得βAR受体脱敏, 信号通路受到阻滞. 目前研究已经发现GRK2在β_1AR碳末端存在丝氨酸簇磷酸化调控位点, GRK2能够通过磷酸化β_1AR募集β-arrestin-1, 继而招募PDE4D抑制β_1AR信号通路[107].

GRK是一类丝氨酸/苏氨酸激酶, 哺乳动物中包含GRK1~GRK7七种亚型, 由保守的氮末端结构域、G蛋白信号同源结构调节域和激酶结构域, 以及较为多样的碳末端区域构成. 根据序列同源性不同, 可将GRK分为三类: 视觉亚家族(GRK1和GRK7)、GRK4亚家族(GRK4、GRK5和GRK6)和βAR激酶亚家族(GRK2

和GRK3)[53]. 在细胞水平定位上, GRK1、GRK4、GRK5、GRK6和GRK7定位于细胞膜, 而GRK2和GRK3则分布于细胞质内. GRK2的氨末端和碳末端以及GRK3的碳末端均存在Gβγ的结合位点, 当GPCR激动引起Gβγ活化后, GRK2和GRK3可向细胞膜募集[108,109]. 在组织水平分布上, GRK1和GRK7主要表达在视网膜感光细胞中, GRK4在睾丸中表达最为丰富, GRK2、GRK3、GRK5和GRK6则不同程度地普遍表达于不同组织中[53]. 心脏中GRK2、GRK3和GRK5表达占主导[110].

关于GRK2在心脏中的作用, 许多研究进行了探索. 利用遗传操纵技术, 研究发现, 尽管GRK2全身敲除导致小鼠胚胎致死[111], 但半敲除小鼠中βAR介导的心脏收缩功能则会增强[112]. 此外, 心肌缺血复灌后过表达GRK2降低了βAR介导的心脏收缩功能并会导致心肌细胞自噬[113]; 而在梗死前或梗死10 d后降低心脏中GRK2的表达则能够增强心脏收缩功能降低死亡率[114]. 在心衰与心肌损伤等病理条件下GRK2的表达会升高[115], 使得GRK2成为心衰疾病治疗中的一个关键靶点. 例如, 利用GRK2碳末端肽段与内源性GRK2竞争Gβγ结合位点以抑制GRK2向膜募集进而抑制其对βAR的脱敏作用, 在动物实验中已经被证实能够有效调控心肌收缩[116,117].

3.2 β-arrestin

β-arrestin是arrestin家族的一种多功能蛋白, 有arrestin1~4四种亚型. arrestin1和4仅在视网膜细胞中表达, 而arrestin2和3(分别称为β-arrestin1和2)在哺乳动物细胞中普遍表达, 这两种亚型在GPCR信号转导中起关键作用. β-arrestin以多种方式调控其相应的GPCR信号通路. 一方面, β-arrestin在受体脱敏中发挥重要作用, 使GPCR与其相关的G蛋白解耦联, 减弱GPCR信号传导. GRK磷酸化GPCR后募集β-arrestin, β-arrestin与G蛋白竞争与GPCR的结合并限制其激活. 此外, β-arrestin能够招募降解酶, 如二酰甘油激酶和磷酸二酯酶, 促进下游第二信使的清除. 另一方面, β-arrestin也参与GPCR内化过程. 与GPCR结合后, β-arrestin通过衔接蛋白(adaptor protein)与网格蛋白(clathrin)结合, 导致GPCR内化[118]. GPCR最终被酶降解或在酸化囊泡中去磷酸化并返回细胞膜. β-arrestin的泛素化对GPCR内化至关重要. 此外, β-arrestin与GPCR结合后, 还能启动不依赖于G蛋白的信号通路, 如激活细胞外调节蛋白激酶(extracellular regulated protein kinases, ERK)信号通路等[119].

β-arrestin1和2在心血管系统所有细胞(包括心肌细胞、成纤维细胞、内皮细胞和传导细胞)的信号转导中都发挥着重要作用[68,120]. β-arrestin1和2具有70%以上的序列相似性和相似的三维结构, 在受体脱敏、内化和信号传导中均发挥作用, 但是其具体功能存在一定差异. 目前研究认为在βAR信号转导中, β-arrestin1可能对心脏有害, 而β-arrestin2可能对心脏有保护作用[118]. 体内和体外研究都证实β-arrestin2以βAR依赖的方式与SERCA2a直接相互作用, 增强SERCA2a活性, 进而增强心肌收缩力[121].

3.3 PDE

PDE是一类由21个不同基因编码的酶家族, 根据序列相似性、调节模式和对以cAMP或cGMP为底物的偏好, 可分为12个家族和100多个亚型. 其中PDE4、PDE7和PDE8特异地以cAMP为底物, PDE5、PDE6和PDE9特异地以cGMP为底物, PDE1、PDE2、PDE3、PDE10和PDE11则与cAMP和cGMP均可结合. 除PDE6、9、10和11外, 大多数PDE亚型在心脏中存在一定程度的表达, 其中占主导的是PDE3和PDE4, 它们能够调控心肌细胞钙信号[122].

PDE4D是心脏中表达丰富的一种亚型, *PDE4D*基因编码9个变体(PDE4D1-9), 具有相同的催化结构域和碳末端, 以及与细胞定位相关的独特的氮末端[122]. PDE4D水解cAMP并调节cAMP在心肌细胞内的水平, 在耦联子处PDE4D也有所活动, 从而参与兴奋-收缩耦联过程中cAMP和钙稳态调控[123,124]. 在心肌细胞中, PKA和PDE4D分布在相同区域, 对于βAR信号在亚细胞部位的持续性、心肌细胞的收缩性和cAMP信号的及时终止至关重要[125]. 在心衰病人心脏中, RyR2复合物中的PDE4D3水平降低, 导致PKA过度磷酸化RyR2, RyR2通道发生钙漏, 从而促进心脏功能障碍并导致心律失常的发生. 小鼠*PDE4D*基因失活会导致进行性心肌病并加速心肌梗死后心力衰竭和心律失常的发生[126].

3.4 β_2AR对β_1AR信号转导的调控

尽管在正常心肌细胞中, β_2AR激活只能对LCC通

道钙内流产生调控，然而，在心力衰竭的心脏细胞中，β_2AR激活会减弱β_1AR信号传导[127]．在β_2AR过表达的转基因小鼠中，心肌细胞收缩能力被自发的β_2AR-cAMP信号上调，但不再能够响应β_1AR刺激[128,129]．由Epi诱导的Takotsubo心肌病，特征表现为心尖收缩抑制，也被归因于β_2AR信号[130]．我们发现，β_2AR通过GRK2磷酸化β_1AR碳末端，并通过β-arrestin-1招募PDE4(图1)，将广域的β_1AR信号阻隔于膜下纳米微区，即β_2AR对β_1AR信号进行越界阻隔(offside compartmentilization)，使得β_1AR像β_2AR一样只能调节细胞膜钙内流，不能调节肌质网钙释放[107](图1)．进一步研究表明，与β_1AR单独激活引起的全细胞效应不同，被β_2AR越界阻隔后β_1AR信号既不调节钙火花的幅度和时空特性，也不调节RyR2对LCC钙火花反应的动力学，但能够通过上调LCC钙内流同步RyR2钙释放．在钙信号转导效率高的正常心肌细胞中，这种钙内流调控的同步化是冗余的，并不能增强收缩力．然而，在心力衰竭等病理条件下，钙信号转导效率降低导致钙内流冗余度降低，兴奋收缩耦联同步化可提高心肌细胞的收缩力[131]．

4　βAR与心脏疾病

在一些病理情况下，βAR信号通路持续激活可能引发一系列不良生理效应，对心脏正常功能产生负面影响，如破坏正常的钙稳态，促进心律失常(cardiac arrhythmias)，加剧心肌缺血再灌注(ischemia-reperfusion, I/R)损伤，促进心肌肥厚(cardiomyocyte hypertrophy)和心力衰竭(heart failure, HF)等疾病的发生和发展．因此，维持βAR信号通路的正常功能对于维护心脏健康至关重要．

4.1　心律失常

临床中，心律失常可分为多种类型，机制也各不相同[132]．过缓性心律失常由窦房结变性与纤维化、房室结传导阻滞等心脏起搏点或传导路径障碍引起；过速性心律失常则包括窦性心动过速、房性心动过速、心房扑动等心脏电信号异常[132,133]．多种心律失常由离子通道基因突变所致，包括先天性长QT综合征(long QT syndrome)、短QT间期综合征(short QT interval syndrome)、Brugada综合征、儿茶酚胺敏感型多态室性心动过速(catecholaminergic polymorphic ventricular tachycardia, CPVT)、特发性室颤(idiopathic ventricular fibrillation)、Wolff-Parkinson-White综合征、致心律失常性心肌病(arrhythmogenic cardiomyopathy)等．缺血性心脏病相关的各种心律失常一般为获得性心律失常[134]．心房颤动(atrial fibrillation)可导致中风或心力衰竭等危及生命的并发症[135]，室性心动过速，特别是室颤则可导致心源性猝死[136]．

βAR持续激活导致心肌细胞钙信号失调，是多种心律失常的重要机制．βAR激活产生的cAMP信号传递至PKA和被cAMP直接激活的交换蛋白(exchange proteins directly activated by cAMP, Epac). Epac激活可激活CaMKII[137](图1). 在βAR持续激活过程中, PKA或CaMKII会过度磷酸化RyR2和PLB, 导致肌质网异常钙泄露[138]．肌质网异常钙泄露使得心肌细胞内钙离子浓度升高，细胞膜上NCX活动增加，心肌细胞产生延迟后去极化(delayed afterdepolarization, DAD)及触发活动(triggered activity, TA)，引起心律失常[139~141]．在CPVT疾病中，RyR2、CSQ2等蛋白的突变时βAR激活期间RyR2钙释放变得更加不稳定．由此产生的自发钙火花通过钙致钙释放的机制再生性地引发临近钙释放位点产生钙火花，从而形成钙波，是CPVT病人心律失常发生的重要机制．近期研究指出，骨桥蛋白(osteopontin)及其受体CD44参与调控Epac介导的钙信号异常及室性心律失常，抑制CD44能够有效减少心力衰竭中室性心律失常的发生，为预防心脏病患者心律失常和心源性猝死提供了新的治疗靶点[139]．

4.2　心肌梗塞与缺血再灌损伤

心肌梗塞在病理学上被定义为由于持续缺血导致的心肌细胞死亡[142]，可能由急性动脉粥样硬化斑块破裂或在没有急性动脉血栓形成的情况下，心肌氧供和/或需求发生改变而引起[143]，是造成成人死亡的主要原因之一，幸存患者发生心力衰竭的风险增加[144]．缺血发作10~15 min内可观察到心肌细胞糖原减少、肌原纤维松弛和肌细胞膜破坏等超微结构改变[145]，在冠状动脉闭塞10 min后可观察到线粒体异常[146]，坏死从心内膜向心外膜逐渐进行[147]．心肌梗塞后渐进性慢性心力衰竭和心输出量降低会导致神经内分泌反应的激活以及肾上腺素能信号的紊乱，引起交感神经系统活动的改变，导致病理性重塑、坏死和细胞凋亡[148]．研究

表明, 心肌梗塞向心力衰竭过程发展中, 交感神经系统过度激活, 心肌细胞βAR密度下降, 血浆儿茶酚胺浓度升高, 左心室逐步扩张, 最终发展为心力衰竭[149].

急性心肌梗塞由冠状动脉突然闭塞引起, 导致相应心肌区域的缺血, 进而导致心肌坏死. 如果不能恢复冠状动脉的血液灌注, 心肌瘢痕的形成将导致心肌不良重塑和心力衰竭. 然而, 冠状动脉恢复灌注却加重和加速心肌损伤, 这一病理过程被称为缺血再灌注损伤[150]. 心肌损伤最初几分钟内, 产生多种来源的氧化应激, 通过多种不同机制介导心肌细胞破坏和死亡; 心肌细胞发生钙超载在心肌再灌注时氧化应激、肌质网损伤、线粒体功能异常中发挥关键作用; 胞内酸化也参与缺血再灌注急性损伤[151]; 炎症反应参与慢性心肌损伤[150,152].

研究表明, 在病人局部心肌缺血2 min后, 血浆儿茶酚胺水平上升[153], 与心血管反射、起源于缺血区的传入神经纤维的激活[154]以及疼痛和焦虑等导致交感神经系统激活相关[153]. 血浆儿茶酚胺水平已被证明与左心室射血分数呈负相关[153], 并与心律失常的发生有关[155,156]. 急性心肌缺血时, 虽然血浆儿茶酚胺不能到达缺血区, 缺血区交感神经末梢活动增加使得缺血区儿茶酚胺浓度远高于血浆儿茶酚胺浓度[153]. 由此导致的肾上腺素受体过度激活会引起后去极化和触发电活动以及心律失常的发生[157,158].

4.3 心肌肥厚和心力衰竭

心力衰竭是由心脏无法充分泵送血液以满足身体需求而引发的疾病, 具有高发病率和高死亡率. 其发生与心脏长期承受压力、瓣膜性心脏病、心肌梗塞、心肌局部缺血、遗传性心脏疾病等有关[159]. 作为对心肌损伤和负荷增加的反应, 心脏最初以心肌细胞体积增大的方式进行代偿性反应以保持正常的泵血功能, 这一过程称为病理性心肌肥厚, 伴随着生化、分子、结构和代谢的变化[160]. 随着时间推移, 心肌的结构和功能重塑会导致心室扩张, 心肌细胞横管系统破坏, 横管与肌质网脱耦联, 肌质网钙泵活性下降, 心肌钙致钙释放效率下降, 收缩功能下降, 最终发展为心力衰竭[159]. 心力衰竭患者的心输出量减少, 进而引起肾脏血流灌注不足、液体和盐滞留, 还会出现呼吸困难、运动耐受性降低、颈静脉压升高和脚踝肿胀等症状[161].

在心肌肥厚和心力衰竭发展过程中, 交感神经系统及βAR信号发挥了关键作用[162]. 心输出量减少引起交感神经系统的代偿性激活, 从而增加了儿茶酚胺循环量以恢复心脏功能. 尽管急性期神经-激素激活能够维持心输出量, 但βAR长期激活后, β-arrestin蛋白介导βAR内化使其表达量下调, βAR还会与G蛋白解耦联发生脱敏, 使得心肌细胞对βAR激活的反应度降低, PKA-cAMP信号减弱, 从而降低心肌收缩力. 研究表明, 心衰病人心室中β_1AR表达量下调62%, 而β_2AR表达量则几乎没有变化[59]. 尽管如此, 有研究指出β_2AR在衰竭心脏中的功能与脱敏相当[163]. 心衰病人心室肌细胞中, G_i信号转导增加, β_2AR与G_i耦联增加[164,165], 而与G_s-AC解耦联[166], 其激活产生cAMP的能力显著下降, 导致心肌收缩效率降低[167]. 目前, 临床上主要使用βAR阻滞剂来治疗心力衰竭, 以防止βAR过度激活, 逆转βAR下调, 改善左心室收缩功能[168].

5 结语

βAR信号通路对心肌细胞钙信号具有重要调控作用, 其功能异常导致心脏疾病的发生. 因此, 了解βAR信号通路对心肌细胞钙信号的调节对深入认识心脏功能的生理调控和研究心脏疾病的应对方案均具有重要意义.

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Regulation of β-adrenergic receptors on cardiomyocyte calcium signaling

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The heart pumps blood rhythmically to the entire body relying on the excitation-contraction coupling initiated by the calcium-induced calcium release process in cardiomyocyte. Sympathetic neurotransmitters bind with β-adrenergic receptors (βARs) to regulate cardiomyocyte calcium signaling as well as the contraction and relaxation function of the heart. Under pathological conditions, abnormal βAR and calcium signaling leads to heart diseases such as arrhythmia, heart failure and ischemia-reperfusion injury. Therefore, elucidating the βAR regulation of calcium signaling in cardiomyocytes is important for understanding heart disease mechanisms and for developing drug treatments.

cardiomyocyte, β-adrenergic receptor, calcium signaling

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