doi: 10.3978/j.issn.2095-6959.2021.08.032
View this article at: https://dx.doi.org/10.3978/j.issn.2095-6959.2021.08.032

·综述·

乳酸 /HCAR1 信号系统的生物学功能研究进展

帅念念[1*]，周佳秀[1*] 综述　田绍文[2]，王波[1]，旷昕[1,3] 审校

(1. 南华大学附属第一医院麻醉科，湖南 衡阳 421001；2. 桂林医学院基础医学院广西脑与认知神经科学重点实验室，广西 桂林 541001；3. 南方医科大学附属龙华区人民医院麻醉科，广东 深圳 518109)

[摘　要]　羟基羧酸受体1(hydroxy-carboxylic acid receptor 1，HCAR1)是一种孤儿G蛋白耦联受体，也是乳酸的特异性受体，广泛分布于中枢和外周组织。近年来，越来越多的研究表明，乳酸/HCAR1信号系统在机体发挥重要作用。乳酸/HCAR1信号系统通过激活下游信号通路，参与内分泌系统、心血管系统、神经系统、免疫系统、肿瘤等相关系统疾病的发生和发展过程。

[关键词]　乳酸；羟基羧酸受体1；GPR81；内分泌系统；神经系统；肿瘤

Research progress in the biological function of lactate/HCAR1 signaling system

SHUAI Niannian[1*], ZHOU Jiaxiu[1*], TIAN Shaowen[2], WANG Bo[1], KUANG Xin[1,3]

(1. Department of Anesthesiology, First Affiliated Hospital of University of South China, Hengyang Hunan 421001; 2. Guangxi Key Laboratory of Brain and Congnitive Neuroscience, Faculty of Basic Medical Sciences, Guilin Medical University, Guilin Guangxi 541001; 3. Department of Anesthesiology, Longhua People's Hospital, Southern Medical University, Shenzhen Guangdong 518109, China)

Abstract　Hydroxy-carboxylic acid receptor 1 (HCAR1) is an orphan G protein-coupled receptor and a specific receptor for lactate, which is widely distributed in central and peripheral tissues. In recent years, more and more studies have shown that lactate/HCAR1 signaling system plays an important role in the body. By activating the downstream signaling pathway, the lactate/HCAR1 signaling system is involved in the occurrence and development of diseases related to endocrine system, cardiovascular system, nervous system, immune system, tumors, etc.

Keywords　lactate; hydroxy-carboxylic acid receptor 1; GPR81; endocrine system; nervous system; tumors

* 为共同第一作者

收稿日期 (Date of reception)：2020–07–04

通信作者 (Corresponding author)：旷昕，Email: kx6924@126.com

基金项目 (Foundation item)：湖南省自然科学基金 (2018JJ3465)。This work was supported by the Hunan Provincial Natural Science Foundation, China (2018JJ3465).

羟基羧酸受体(hydroxy-carboxylic acid receptor，HCAR)1属于G蛋白偶联受体，因其能被能量代谢中间产物羟基羧酸激活而得名[1]。HCAR家族包括HCAR1、HCAR2和HCAR3，分别称为GPR81、GPR109A和GPR109B。2001年，Lee等[2]通过基本局部比对搜索工具(Basic Local Alignment Search Tool，BLAST)分析首次在人类脑垂体中发现孤儿受体HCAR1。随后，Liu等[3]发现：HCAR1在脂肪组织中高表达，并证实乳酸作为HCAR1的内源性配体，通过下调环磷酸腺苷(cyclic adenosine monophosphate，cAMP)水平抑制脂肪组织分解。近年来发现，乳酸作为信号分子在机体中发挥着越来越重要的作用，乳酸/HCAR1信号系统也逐渐受到关注。本文综述了乳酸/HCAR1信号系统在内分泌系统、心血管系统、神经系统、免疫系统与肿瘤中的作用，为阐明疾病的发生和发展机制及治疗提供新思路。

1 乳酸 /HCAR1 信号系统概述

1.1 乳酸的产生及作用

乳酸是糖酵解代谢产物。当机体处于缺氧状态时，细胞通过无氧糖酵解产生乳酸和ATP，满足机体代谢需要。而在正常氧分压下，细胞也可以通过有氧糖酵解产生乳酸[4]。有氧糖酵解通常发生在肿瘤细胞、骨骼肌细胞和星形胶质细胞中，其代谢产生的乳酸可以通过单羧酸转运蛋白(monocarboxylate transporters，MCTs)转运至其他细胞，作为能量底物进行三羧酸循环和氧化磷酸化，调节机体能量代谢，也可以通过自分泌或旁分泌途径作用于乳酸受体HCAR1或其他相关受体，以信号分子的形式调节细胞活动[5]。

1.2 HCAR1 的结构特征

HCAR1属于G蛋白耦联受体，由7次跨膜结构域、胞内C端、胞外N端、3个胞内环和3个胞外环组成。早在2011年，Kuei等[6]通过对比人类和斑马鱼的HCAR1氨基酸序列发现：HCAR1在不同物种间具有很多相似序列，这种进化保守性提示HCAR1在机体发挥重要作用，也为研究HCAR1提供了良好的契机。人类HCAR1由346个氨基酸组成，分子质量为40~45 kD。建模和突变分析显示：HCAR1的Arg71、Arg99、Glu166和Arg240是与乳酸结合的重要位点，且跨膜2区的Arg71、第2个胞外环C165-E166-S167-F168区域和细胞外6个Cys残基对HCAR1的正常功能起着至关重要的作用[6]。

1.3 HCAR1 的组织分布

HCAR1主要表达在白色和棕色脂肪组织，其他组织如骨骼肌、肾、肝、大脑、胃肠道等也发现少量HCAR1的表达[3,7]。另外，研究[8]发现：HCAR1在各种肿瘤组织和肿瘤细胞系中表达上调，提示HCAR1对肿瘤细胞的生长和发育至关重要。

2 乳酸 /HCAR1 信号系统的生物学功能

2.1 乳酸 /HCAR1 信号系统与内分泌系统

乳酸/HCAR1信号系统能间接感知外周葡萄糖浓度，调节糖脂代谢。Ahmed等[9]发现：细胞外葡萄糖水平增加会引起脂肪组织胰岛素依赖性葡萄糖摄取增加，随后葡萄糖在细胞内转化为乳酸，并释放至胞外，通过激活脂肪细胞表面HCAR1，下调cAMP水平，从而负反馈抑制脂肪分解，平衡葡萄糖与脂质之间的能量代谢。

HCAR1介导的对脂解反应的抑制对一些代谢性疾病同样具有重要意义。脂质在非脂肪组织中的积累是胰岛素抵抗、非酒精性脂肪肝和血脂异常的主要驱动因素[10]，且血浆游离脂肪酸水平升高可抑制胰岛素介导的内源性葡萄糖摄取，导致血糖升高和胰岛β细胞功能障碍[11]。故激活脂肪组织中的HCAR1，抑制脂质降解、降低血浆游离脂肪酸水平[12-14]可能是逆转胰岛素抵抗相关代谢性疾病的一种重要手段。另外，Kwon等[15]在高脂饮食小鼠模型中发现：激活HCAR1能增加脂肪组织对葡萄糖的摄取，显著降低血糖水平，为糖尿病的防治提供新思路。

乳酸/HCAR1信号系统还可以抑制胃饥饿素的分泌，调节机体能量代谢。胃饥饿素是由胃黏膜细胞分泌的一种肽类激素，在调控进食、葡萄糖代谢、血糖、体重等方面发挥着重要作用[16]。血浆胃饥饿素水平在餐前升高，餐后迅速下降[17]。研究[18]发现：HCAR1在胃黏膜细胞高表达，且乳酸及HCAR1激动剂呈剂量依赖性抑制胃饥饿素分泌。随后，体外研究[19]显示：乳酸通过激活HCAR1/Gi信号通路下调cAMP水平，抑制胃饥饿素分泌。胃饥饿素分泌减少不仅可以降低食欲，减少摄食行为[16]，还能促进胰岛素分泌，改善高脂饮食小鼠

葡萄糖耐受不良[20]。乳酸/HCAR1信号系统能从多个角度调节糖脂代谢，其具体分子机制有待进一步研究。

2.2 乳酸 /HCAR1 信号系统与心血管系统

乳酸能够通过作用于乳酸特异性受体HCAR1，促进血管收缩，增加动脉血压。Wallenius等[21]研究显示：在不同动物模型中，静脉内注射HCAR1激动剂都可以增加肾入球小动脉血管阻力，升高动脉血压，且这种升压效应与内皮素-1(endothelin 1，ET-1)水平增加有关。Jones等[22]的研究也表明：在雄性野生型小鼠中，静脉输注HCAR1激动剂可以导致收缩压和舒张压快速持续升高，同时引起肾动脉血流灌注和肾小球滤过率减少。HCAR1激动剂可以增加血浆ET-1水平，而ET-1是最有效的血管活性因子，且在肾脏浓度最高[23]，表明在剧烈运动、组织缺血缺氧或损伤等应激情况下，细胞外升高的乳酸通过HCAR1参与机体稳态的调节[21]，即在应激情况下，血液从肾脏分流，支持机体重要脏器的血液供应。目前，有关HCAR1与ET系统的分子机制尚未阐明。Walleniu等[21]推测：局部ET-1释放增加可能与内皮细胞HCAR1激活导致的cAMP水平降低有关。

此外，激活HCAR1还可以降低氧化应激，抑制单核细胞黏附于血管内皮细胞，下调单核细胞趋化蛋白-1(monocyte chemoattractant protein-1，MCP-1)、高迁移率族蛋白B1(high mobility group box 1，HMGB1)及炎症因子白细胞介素(interleukin，IL)-6、IL-8的表达，发挥抗动脉粥样硬化的作用[24]。

2.3 乳酸 /HCAR1 信号系统与神经系统

在中枢神经系统，HCAR1主要定位于海马和小脑兴奋性神经元突触后膜，同时，大脑血管内皮细胞和星形胶质细胞也能检测到少量HCAR1的表达[25]。乳酸/HCAR1信号系统能降低神经元兴奋性。2013年，Bozzo等[26]首次证明了乳酸通过与其受体结合，降低大脑自发钙峰频率，抑制神经元网络活性。这种抑制作用与乳酸激活HCAR1导致腺苷酸环化酶(adenylyl cyclase，AC)/cAMP/蛋白激酶A(protein kinase A，PKA)信号通路下调[27]、钠通道开放延迟[28]及内向整流钾通道激活[29]有关。有报道[28]称：乳酸对神经元兴奋性调节具有双向作用，即低浓度(5 mM)乳酸或激活HCAR1抑制神经元兴奋性，高浓度(30 mmol/L)乳酸增加神经元兴奋性。大脑乳酸生理浓度范围在1.3~5.1 mmol/L[30]，提示正常情况下乳酸可能通过HCAR1负反馈调节神经元兴奋性，但在病理条件中，乳酸则表现为代谢失偿。另外，乳酸与HCAR1结合的半数有效浓度(50% effective concentration，EC50)在1.3~5.0 mmol/L[3,14]，进一步强调生理范围的乳酸对HCAR1的作用。

乳酸/HCAR1信号系统也具有神经保护作用。Castillo等[31]发现：在大脑中动脉闭塞模型中，海马、大脑皮层和纹状体HCAR1表达增加，且*D*-乳酸(非代谢性HCAR1部分激动剂)和3,5-二羟基苯甲酸(3,5-dihydroxybenzoic acid，3,5-DHBA；非代谢性HCAR1选择性激动剂)能降低缺血皮层梗死面积，减少神经元细胞死亡。Vohra等[32]对视网膜胶质细胞的研究表明：葡萄糖剥夺后，HCAR1表达上调，乳酸通过激活HCAR1增加葡萄糖代谢和线粒体功能，提高细胞存活率。最近一项研究[33]显示：乳酸通过星形胶质细胞HCAR1/β-arrestin2通路增加Arc/arg3.1蛋白的表达，减少谷氨酸暴露引起的钙离子内流，间接增加星形胶质细胞对谷氨酸的清除，保护星形胶质细胞和神经元免受谷氨酸毒性损伤。此外，乳酸/HCAR1信号系统还可以抑制小胶质细胞NOD样受体蛋白3(NOD-like receptor protein 3，NLRP3)炎症小体形成和IL-1释放，减轻神经炎症反应[34]，激活血管内皮细胞细胞外信号调节激酶(extracellular signal-regulated kinase，ERK)1/2和Akt信号通路，增加海马血管内皮生长因子的表达和血管生成[35]。上述研究表明：乳酸/HCAR1信号系统通过不同途径发挥神经保护功能，从而参与神经系统疾病的发生发展过程。

乳酸/HCAR1信号系统还能增强记忆巩固。Scavuzzo等[36]发现：在记忆巩固阶段，大鼠皮下注射*L*-乳酸、*D*-乳酸和3,5-DHBA都可以增强长时程记忆。有趣的是，在学习阶段，只有*L*-乳酸能增强大鼠学习记忆，强调了乳酸调节学习记忆的神经生理学机制的复杂性。乳酸/HCAR1信号系统增加Arc/arg3.1蛋白表达[33]，可增强突触可塑性和长时程记忆巩固[37]。且Lee等[38]研究表明：乳酸/HCAR1信号系统通过Wnt/β-catenin信号通路促进肠道干细胞分化，而Wnt信号已被证明对成人大脑神经发生具有积极的调节作用[39]，提示在中枢神经系统，乳酸/HCAR1可能通过Wnt/β-catenin信号通路促进海马神经发生，进而促进记忆巩固。

2.4 乳酸 /HCAR1 信号系统与免疫系统

乳酸通过作用于HCAR1，负反馈抑制炎症反应。Hoque等[40-41]研究表明：乳酸作用于HCAR1，抑制单核巨噬细胞Toll样受体4(toll-like receptor 4，TLR4)介导的NLRP3炎症小体形成和炎症因子的产生，减轻急性胰腺炎和急性肝损伤的程度。而HCAR1基因缺失的小鼠辅助T细胞(T helper cell，Th)1/Th17细胞分化增加，炎症因子产生增多，肠道炎症易感性增加[42]。在分娩过程中，子宫平滑肌无氧糖酵解产生的乳酸作用于HCAR1，下调促炎基因的表达[43]。而暴露于脂多糖会降低大脑血管内皮细胞上HCAR1的表达，升高炎症因子水平，从而诱发神经炎症[44]。

2.5 乳酸 /HCAR1 信号系统与肿瘤

肿瘤细胞高表达HCAR1，乳酸通过激活HCAR1，对肿瘤细胞的生存和生长起重要作用。Roland等[8]发现：乳酸激活HCAR1会增加肿瘤细胞过氧化物酶体增殖物激活受体γ辅激活因子1α(peroxisome proliferator-activated receptor γ co-activator 1α，PGC-1α)、MCTs及其伴侣蛋白CD147的表达，促进肿瘤细胞对乳酸的摄取和氧化代谢，促进癌细胞的生长。Lee等[45]也发现：乳酸通过作用于乳腺癌细胞表面HCAR1，激活磷脂酰肌醇3-激酶 (phosphoinositide 3-kinase，PI3K)/Akt/cAMP反应元件结合蛋白(cAMP response element binding protein，CREB)信号通路，增加双调蛋白的产生和血管生成，进而促进乳腺癌细胞的增殖、迁移和侵袭。

乳酸/HCAR1信号系统参与肿瘤细胞的免疫逃逸，同样有助于肿瘤细胞的存活。Feng等[46]研究表明：HCAR1的激活会抑制肺癌细胞内cAMP/PKA信号通路，导致转录因子含PDZ结合基序的转录共激活因子(transcriptional coactivator with PDZ-binding motif，TAZ)/转录增强相关结构域(transcriptional enhanced associate domain，TEAD)向程序性死亡配体1(programmed cell death protein 1 ligand，PD-L1)启动子转移，诱导PD-L1表达。随后，作者将表达HCAR1的肺癌细胞与T细胞共培养发现：乳酸/HCAR1诱导的PD-L1水平升高会引起γ干扰素产生减少和T细胞凋亡，从而保护肿瘤细胞免受攻击。Brown及其同事[47]发现：乳酸通过旁分泌作用于肿瘤基质树突状细胞膜表面的HCAR1，可能也是癌细胞逃避免疫的关键。通过激活HCAR1，乳酸抑制树突状细胞表面主要组织相容性复合体II(major histocompatibility complex II，MHC II)分子表达和促炎因子IL-6和IL-12分泌，阻止癌细胞特异性抗原在免疫细胞之间的呈递。

另外，HCAR1激活还会增加肿瘤耐药性。Wagner等[48]研究发现：激活宫颈癌细胞中的HCAR1会增加DNA修复能力，其机制与HCAR1激活导致DNA修复蛋白乳腺癌易感基因1(breast cancer susceptibility gene 1，BRCA1)、nibrin和DNA依赖性蛋白激酶催化亚基(DNA-dependent protein kinase catalytic subunit，DNA-PKcs)表达增加有关[49]。抗癌化学治疗药物的作用机制之一是诱导肿瘤细胞DNA双链断裂，故降低HCAR1的表达可能有助于降低细胞耐药性。此外，HCAR1激活还可以诱导ATP结合盒B亚家族1转运蛋白(ATP-binding cassette subfamily B member 1，ABCB1)表达，增加宫颈癌细胞对化学治疗药物的外排和细胞耐药性[50]。

肿瘤细胞HCAR1表达上调的机制仍不清楚。最近，Xie等[51]发现：HCAR1在肿瘤细胞中的表达可以由乳酸本身驱动。乳酸上调转录因子Snail，诱导Snail/果蝇zeste基因增强子的人类同源物2(enhancer of zeste homolog 2，EZH2)/信号转导转录激活因子3(signal transducer and activator of transcription 3，STAT3)复合体形成，从而与HCAR1启动子结合并促进其表达。然而是否有其他因子参与HCAR1表达，有待进一步研究。

2.6 其他

乳酸/HCAR1信号系统可以通过丝裂原激活蛋白激酶激酶(mitogen-activated protein kinase kinase，MEK)/ERK通路，增加肌管直径[52]，还可以通过HCAR1/蛋白激酶C(protein kinase C，PKC)/Akt通路增强成骨细胞分化[53]。这些研究表明：乳酸可以促进机体生长，并从不同角度证明了运动对人体的重要意义。乳酸/HCAR1信号系统的生物学功能机制见图1[54]。

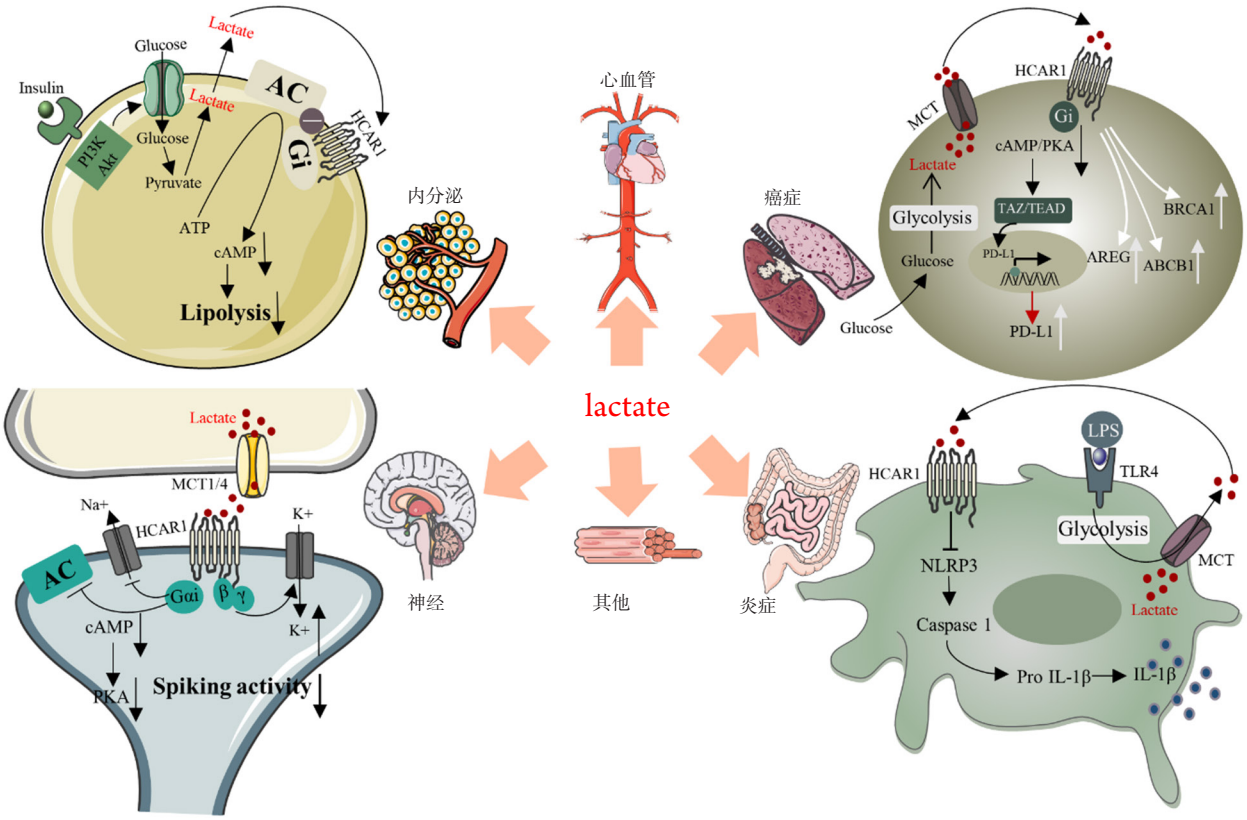

图1 乳酸/HCAR1信号系统作用机制图

Figure 1 Mechanism involved in lactictate/HCAR1 signaling system

AREG：双调蛋白；LPS：脂多糖；TLR4：Toll样受体4。

AREG: amphiregulin; LPS: lipopolysaccharide; TLR4: Toll-like receptor 4.

3 结语

乳酸/HCAR1信号系统在机体内分布广泛，通过调节能量代谢、抑制脂质分解、促进血管收缩、降低细胞氧化应激、降低神经元兴奋性、减少神经元死亡、抑制炎症反应和促进肿瘤生长等可能参与糖尿病、肥胖、高血压、动脉粥样硬化、癫痫、缺血性脑损伤、阿尔茨海默病和肿瘤等多种疾病的生理病理过程。目前，对于HCAR1的研究尚处于探索阶段，后续研究有待进一步明确乳酸/HCAR1信号系统在机体的生物学功能及其下游信号通路，以及其相关作用机制，如HCAR1的调控机制、乳酸与HCAR1之间的相互调节、乳酸在能量代谢和信号分子之间的平衡、HCAR1在不同组织细胞的作用等，并在相关疾病模型中进行验证，从而开发新的有效措施延缓疾病的发生发展过程，为疾病机制探索和治疗方案优化提供参考。

参考文献

1. Blad CC, Ahmed K, IJzerman AP, et al. Biological and pharmacological roles of HCA receptors[J]. Adv Pharmacol, 2011, 62: 219-250.
2. Lee DK, Nguyen T, Lynch KR, et al. Discovery and mapping of ten novel G protein-coupled receptor genes[J]. Gene, 2001, 275(1): 83-91.
3. Liu C, Wu J, Zhu J, et al. Lactate inhibits lipolysis in fat cells through activation of an orphan G-protein-coupled receptor, GPR81[J]. J Biol Chem, 2009, 284(5): 2811-2822.
4. Magistretti PJ, Allaman I. Lactate in the brain: from metabolic end-product to signalling molecule[J]. Nat Rev Neurosci, 2018, 19(4): 235-249.
5. Brooks GA. Lactate as a fulcrum of metabolism[J]. Redox Biol, 2020, 35: 101454.
6. Kuei C, Yu J, Zhu J, et al. Study of GPR81, the lactate receptor, from distant species identifies residues and motifs critical for GPR81

functions[J]. Mol Pharmacol, 2011, 80(5): 848-858.

7. Ge H, Weiszmann J, Reagan JD, et al. Elucidation of signaling and functional activities of an orphan GPCR, GPR81[J]. J Lipid Res, 2008, 49(4): 797-803.
8. Roland CL, Arumugam T, Deng D, et al. Cell surface lactate receptor GPR81 is crucial for cancer cell survival[J]. Cancer Res, 2014, 74(18): 5301-5310.
9. Ahmed K, Tunaru S, Tang C, et al. An autocrine lactate loop mediates insulin-dependent inhibition of lipolysis through GPR81[J]. Cell Metab, 2010, 11(4): 311-319.
10. Samuel VT, Shulman GI. Mechanisms for insulin resistance: common threads and missing links[J]. Cell, 2012, 148(5): 852-871.
11. Weir GC. Glucolipotoxicity, β-cells, and diabetes: The emperor has no clothes[J]. Diabetes, 2020, 69(3): 273-278.
12. Rooney K, Trayhurn P. Lactate and the GPR81 receptor in metabolic regulation: Implications for adipose tissue function and fatty acid utilisation by muscle during exercise[J]. Br J Nutr, 2011, 106(9): 1310-1316.
13. Sakurai T, Davenport R, Stafford S, et al. Identification of a novel GPR81-selective agonist that suppresses lipolysis in mice without cutaneous flushing[J]. Eur J Pharmacol, 2014, 727: 1-7.
14. Cai TQ, Ren N, Jin L, et al. Role of GPR81 in lactate-mediated reduction of adipose lipolysis[J]. Biochem Biophys Res Commun, 2008, 377(3): 987-991.
15. Kwon E, Yoo T, Joung HY, et al. Hydrocarboxylic acid receptor 1 in BAT regulates glucose uptake in mice fed a high-fat diet[J]. PLoS One, 2020, 15(1): e0228320.
16. Yanagi S, Sato T, Kangawa K, et al. The homeostatic force of ghrelin[J]. Cell Metab, 2018, 27(4): 786-804.
17. Castillo-Armengol J, Fajas L, Lopez-Mejia IC. Inter-organ communication: A gatekeeper for metabolic health[J]. EMBO Rep, 2019, 20(9): e47903.
18. Engelstoft MS, Park WM, Sakata I, et al. Seven transmembrane G protein-coupled receptor repertoire of gastric ghrelin cells[J]. Mol Metab, 2013, 2(4): 376-392.
19. Koyama H, Iwakura H, Dote K, et al. Comprehensive profiling of GPCR expression in ghrelin-producing cells[J]. Endocrinology, 2016, 157(2): 692-704.
20. Dezaki K, Sone H, Koizumi M, et al. Blockade of pancreatic islet-derived ghrelin enhances insulin secretion to prevent high-fat diet-induced glucose intolerance[J]. Diabetes, 2006, 55(12): 3486-3493.
21. Wallenius K, Thalén P, Björkman JA, et al. Involvement of the metabolic sensor GPR81 in cardiovascular control[J]. JCI Insight, 2017, 2(19): e92564.
22. Jones NK, Stewart K, Czopek A, et al. Endothelin-1 mediates the systemic and renal hemodynamic effects of GPR81 activation[J]. Hypertension, 2020, 75(5): 1213-1222.
23. Mitchell T, De Miguel C, Gohar EY. Sex differences in redox homeostasis in renal disease[J]. Redox Biol, 2020, 31: 101489.
24. Sun Z, Han Y, Song S, et al. Activation of GPR81 by lactate inhibits oscillatory shear stress-induced endothelial inflammation by activating the expression of KLF2[J]. IUBMB Life, 2019, 71(12): 2010-2019.
25. Lauritzen KH, Morland C, Puchades M, et al. Lactate receptor sites link neurotransmission, neurovascular coupling, and brain energy metabolism[J]. Cereb Cortex, 2014, 24(10): 2784-2795.
26. Bozzo L, Puyal J, Chatton JY. Lactate modulates the activity of primary cortical neurons through a receptor-mediated pathway[J]. PLoS One, 2013, 8(8): e71721.
27. de Castro Abrantes H, Briquet M, Schmuziger C, et al. The lactate receptor HCAR1 modulates neuronal network activity through the activation of Gα and Gβγ subunits[J]. J Neurosci, 2019, 39(23): 4422-4433.
28. Herrera-López G, Galván EJ. Modulation of hippocampal excitability via the hydroxycarboxylic acid receptor 1[J]. Hippocampus, 2018, 28(8): 557-567.
29. Jorwal P, Sikdar SK. Lactate reduces epileptiform activity through HCA1 and GIRK channel activation in rat subicular neurons in an in vitro model[J]. Epilepsia, 2019, 60(12): 2370-2385.
30. Abi-Saab WM, Maggs DG, Jones T, et al. Striking differences in glucose and lactate levels between brain extracellular fluid and plasma in conscious human subjects: Effects of hyperglycemia and hypoglycemia[J]. J Cereb Blood Flow Metab, 2002, 22(3): 271-279.
31. Castillo X, Rosafio K, Wyss MT, et al. A probable dual mode of action for both L-and D-lactate neuroprotection in cerebral ischemia[J]. J Cereb Blood Flow Metab, 2015, 35(10): 1561-1569.
32. Vohra R, Aldana BI, Waagepetersen H, et al. Dual properties of lactate in müller cells: The effect of GPR81 activation[J]. Invest Ophthalmol Vis Sci, 2019, 60(4): 999-1008.
33. Ma K, Ding X, Song Q, et al. Lactate enhances Arc/arg3.1 expression through hydroxycarboxylic acid receptor 1-β-arrestin2 pathway in astrocytes[J]. Neuropharmacology, 2020, 171: 108084.
34. Harun-Or-Rashid M, Inman DM. Reduced AMPK activation and increased HCAR activation drive anti-inflammatory response and neuroprotection in glaucoma[J]. J Neuroinflammation, 2018, 15(1): 313.
35. Morland C, Andersson KA, Haugen ØP, et al. Exercise induces cerebral VEGF and angiogenesis via the lactate receptor HCAR1[J]. Nat Commun, 2017, 8: 15557.
36. Scavuzzo CJ, Rakotovao I, Dickson CT. Differential effects of L-and D-lactate on memory encoding and consolidation: Potential role of HCAR1 signaling[J]. Neurobiol Learn Mem, 2020, 168: 107151.
37. Gao X, Castro-Gomez S, Grendel J, et al. Arc/Arg3.1 mediates a critical

period for spatial learning and hippocampal networks[J]. Proc Natl Acad Sci USA, 2018, 115(49): 12531-12536.

38. Lee YS, Kim TY, Kim Y, et al. Microbiota-derived lactate accelerates intestinal stem-cell-mediated epithelial development[J]. Cell Host Microbe, 2018, 24(6): 833-846.e6.
39. Kase Y, Otsu K, Shimazaki T, et al. Involvement of p38 in age-related decline in adult neurogenesis via modulation of Wnt signaling[J]. Stem Cell Reports, 2019, 12(6): 1313-1328.
40. Hoque R, Farooq A, Ghani A, et al. Lactate reduces liver and pancreatic injury in Toll-like receptor- and inflammasome-mediated inflammation via GPR81-mediated suppression of innate immunity[J]. Gastroenterology, 2014, 146(7): 1763-1774.
41. Lerch MM, Conwell DL, Mayerle J. The anti-inflammasome effect of lactate and the lactate GPR81-receptor in pancreatic and liver inflammation[J]. Gastroenterology, 2014, 146(7): 1602-1605.
42. Ranganathan P, Shanmugam A, Swafford D, et al. GPR81, a cell-surface receptor for lactate, regulates intestinal homeostasis and protects mice from experimental colitis[J]. J Immunol, 2018, 200(5): 1781-1789.
43. Madaan A, Nadeau-Vallée M, Rivera JC, et al. Lactate produced during labor modulates uterine inflammation via GPR81 (HCA1)[J]. Am J Obstet Gynecol, 2017, 216(1): 60.e1-60.e17.
44. Boitsova EB, Morgun AV, Osipova ED, et al. The inhibitory effect of LPS on the expression of GPR81 lactate receptor in blood-brain barrier model in vitro[J]. J Neuroinflammation, 2018, 15(1): 196.
45. Lee YJ, Shin KJ, Park SA, et al. G-protein-coupled receptor 81 promotes a malignant phenotype in breast cancer through angiogenic factor secretion[J]. Oncotarget, 2016, 7(43): 70898-70911.
46. Feng J, Yang H, Zhang Y, et al. Tumor cell-derived lactate induces TAZ-dependent upregulation of PD-L1 through GPR81 in human lung cancer cells[J]. Oncogene, 2017, 36(42): 5829-5839.
47. Brown TP, Bhattacharjee P, Ramachandran S, et al. The lactate receptor GPR81 promotes breast cancer growth via a paracrine mechanism involving antigen-presenting cells in the tumor microenvironment[J]. Oncogene, 2020, 39(16): 3292-3304.
48. Wagner W, Ciszewski WM, Kania KD. L-and D-lactate enhance DNA repair and modulate the resistance of cervical carcinoma cells to anticancer drugs via histone deacetylase inhibition and hydroxycarboxylic acid receptor 1 activation[J]. Cell Commun Signal, 2015, 13: 36.
49. Wagner W, Kania KD, Ciszewski WM. Stimulation of lactate receptor (HCAR1) affects cellular DNA repair capacity[J]. DNA Repair (Amst), 2017, 52: 49-58.
50. Wagner W, Kania KD, Blauz A, et al. The lactate receptor (HCAR1/GPR81) contributes to doxorubicin chemoresistance via ABCB1 transporter up-regulation in human cervical cancer HeLa cells[J]. J Physiol Pharmacol, 2017, 68(4): 555-564.
51. Xie Q, Zhu Z, He Y, et al. A lactate-induced Snail/STAT3 pathway drives GPR81 expression in lung cancer cells[J]. Biochim Biophys Acta Mol Basis Dis, 2020, 1866(1): 165576.
52. Ohno Y, Oyama A, Kaneko H, et al. Lactate increases myotube diameter via activation of MEK/ERK pathway in C2C12 cells[J]. Acta Physiol (Oxf), 2018, 223(2): e13042.
53. Wu Y, Wang M, Zhang K, et al. Lactate enhanced the effect of parathyroid hormone on osteoblast differentiation via GPR81-PKC-Akt signaling[J]. Biochem Biophys Res Commun, 2018, 503(2): 737-743.
54. Lundø K, Trauelsen M, Pedersen SF, et al. Why warburg works: Lactate controls immune evasion through GPR81[J]. Cell Metab, 2020, 31(4): 666-668.

本文引用： 帅念念, 周佳秀, 田绍文, 王波, 旷昕. 乳酸/HCAR1信号系统的生物学功能研究进展[J]. 临床与病理杂志, 2021, 41(8): 1925-1931. doi: 10.3978/j.issn.2095-6959.2021.08.032

Cite this article as: SHUAI Niannian, ZHOU Jiaxiu, TIAN Shaowen, WANG Bo, KUANG Xin. Research progress in the biological function of lactate/HCAR1 signaling system[J]. Journal of Clinical and Pathological Research, 2021, 41(8): 1925-1931. doi: 10.3978/j.issn.2095-6959.2021.08.032