doi: 10.13241/j.cnki.pmb.2018.09.007

Orexin-A 对大鼠胃功能的影响 *

田 彬[1,2] 郝贺玲[1] 杨丹丹[1] 高胜利[1] 徐 珞[1△]

（1 青岛大学医学院病理生理学教研室 山东 青岛 266021；2 菏泽家政职业学院外科教研室 山东 菏泽 274000）

摘要 目的：探讨 Orexin-A 对大鼠胃功能的影响。**方法：**通过大鼠迷走神经复合体微量注射 Orexin-A 后，观察大鼠胃运动、胃液和胃酸分泌的变化。**结果：**DVC 微量注射 Orexin-A 后，大鼠胃收缩幅度以及收缩频率明显升高，且呈明显剂量依赖关系(P<0.05)，SB334867 可显著阻断 Orexin-A 对促胃运动效应(P＜0.05)。DVC 微量注射 orexin-A 后，大鼠胃液及胃酸分泌且呈剂量依赖性增加(P<0.05)。**结论：**迷走神经复合体微量注射 Orexin-A 能影响胃的运动以及胃内体液的分泌。

关键词：Orexin-A；迷走神经复合体；胃运动；胃液

中图分类号：R-33；R322.8 **文献标识码：**A **文章编号：**1673-6273(2018)09-1633-04

Effects of Orexin-A on the Stomach Function of Rats*

TIAN Bin[1,2], HAO He-ling[1], YANG Dan-dan[1], GAO Sheng-li[1], XU Luo[1△]

(1 Dept. of Pathophysiology, Medical College of Qingdao University, Qingdao, Shandong, 266021, China;

2 Department of surgery; Heze Career Academy, Heze, Shandong, 274000, China)

ABSTRACT Objective: To explore the effect of microinjection of orexin-A into vagal complex (DVC) on the gastric function of rats. **Methods:** Orexin-A was microinjected into the DVC, the changes of gastric motility and gastric juice or gastric acid secretion were observed. **Results:** After the microinjection of orexin-A into DVC, the amplitude and frequency of gastric motility were significantly increased in a dose-dependent manner. SB334867 prevented Orexin-A-induced changes of gastric motility (P<0.05). After the microinjection of orexin-A into DVC, the secretion of gastric juice and gastric acid were significantly increased in a dose-dependent manner (P<0.05). **Conclusion:** Orexin-A could affect gastric motility and the secretion of gastric fluid.

Key words: Orexin-A; DVC; Gastric motility; Gastric fluid

Chinese Library Classification (CLC): R-33; R322.8 Document code: A

Article ID: 1673-6273(2018)09-1633-04

前言

Orexins(Orexin-A 和 Orexin-B)是在下丘脑外侧区发现的与食欲相关且来自于同一前体的神经肽[1,2]。Orexins 神经元纤维广泛投射至中枢神经系统，其中重要区域如下丘脑室旁核、中央内侧核、脑干和脊髓等。研究表明 Orexin 系统，尤其是 Orexin-A 具有广泛的生理作用，参与摄食、能量代谢、睡眠 - 觉醒、胃肠运动、药物奖赏及心血管反应等生理活动的调节[3,4]。研究表明 orexin-A 可自发调节大鼠胃收缩[5]。Orexin-A 静脉注射刺激大鼠胃酸分泌和增强胃肠蠕动[5-8]。中枢给药 orexin-A 增加胃排空率和消化间移行性复合运动(MMC)III 期的频率[5]。迷走神经复合体(DVC)包含孤束核(NTS)、迷走神经背核(DMV)和极后区(AP)，是调控胃运动的重要副交感初级中枢[9]。本研究采用在体胃运动观察 DVC 中 Orexin-A 对胃运动以及胃体液的影响。

1 材料与方法

1.1 实验动物

60 只健康成年雄性 Wistar 大鼠(250～350 g)饲养于动物房，标准饲养环境：室温 22～26 ℃，24 h 光照循环，饮食未加限制，依照实验室标准进食。所有实验均遵从《青岛大学实验动物保护和使用管理办法》进行。

1.2 实验方法

1.2.1 **胃运动实验** 30 只大鼠随机分为 5 组(n=6)，大鼠 DVC 注射：(1) 0.5 μg/0.5 μ Lorexin-A 组；(2) 5.0 μg/0.5 μL orexin-A 组；(3) 5.0 μg/0.5 μL SB334867 组；(4) (0.5 μg orexin-A+5.0 μg SB334867)/0.5 μL 组；(5) 0.5 μL 生理盐水(NS)组。术前大鼠禁食 18 h 后进行腹腔麻醉(硫酸仲丁巴比妥：100～150 mg/kg)，待大鼠完全麻醉后，将其仰卧于操作台，切开腹部，将压力传感器沿着环形肌的方向缝在距幽门 0.5 cm 处的胃窦浆膜面，固定于颈部，缝合切口。术后注意观察动物的疼痛和应激反应，待大鼠恢复正常后，方可进行下一步实验。参照 Paxinos & Watson 大鼠脑立体图谱定位 DVC 然后置管。微量注射器用硅胶管与不锈钢内套管相连，用微量进样器抽取药物缓慢注射至 DVC。

* 基金项目：国家自然科学基金项目(81470815,81270460,81500414)；山东省优秀中青年科学基金项目(BS2014YY009)；青岛市科技局项目(14-2-3-3-nsh)

作者简介：田彬(1983-)，硕士研究生，主要研究方向：能量代谢障碍基础与临床，电话：0532-82991713，E-mail: 391002047@qq.com

△ 通讯作者：徐珞，E-mail: xu.luo@163.com

(收稿日期：2017-05-28 接受日期：2017-06-23)

实验前大鼠禁食 18 h。先将实验大鼠置于实验环境中适应一段时间，待大鼠适应实验环境再进行实验。使用胃运动生理仪器记录胃运动的改变，记录稳定胃运动 30 min 后开始注射药物，注射药物后观察胃运动 60 min。胃运动的改变以变化率表示。

$$\text{胃收缩幅度或频率变化率} = \frac{\text{注药后幅度或频率} - \text{注药前幅度或频率}}{\text{注药后幅度或频率}} \times 100\%$$

1.2.2 **胃体液实验** 30 只大鼠随机分为 5 组(n=6)，大鼠 DVC 注射：(1) 0.5 μg/0.5 μL orexin-A 组；(2) 5.0 μg/0.5 μL orexin-A 组；(3) 5.0 μg/0.5 μL SB334867 组；(4) (0.5 μg orexin-A+5.0 μg SB334867)/0.5 μL 组；(5) 0.5 μL 生理盐水(NS)组。采用幽门结扎法收集胃液[10]。大鼠乙醚短暂麻醉，沿腹中线剑突下切开一小口，暴露幽门，沿幽门括约肌丝线结扎，关腹，DVC 给药 3 h 后过量乙醚麻醉处死大鼠，迅速取胃，沿胃大弯剪开胃壁，快速收集大鼠胃中的胃液，检测胃酸的分泌量。首先测量出收集的胃液量，再取少量胃液放置在烧杯中，用酸碱滴定法计算出胃酸的浓度，胃酸的分泌量 = 胃酸浓度 X 所收集的胃液量。

1.3 统计学分析

所有数据均用 Prism 5.0 进行统计分析，数据均以 $\bar{x}\pm s$ 表示，多组间比较采用单因素方差分析，组间两两比较采用 t 检验，以 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 DVC 注射 orexin-A 对大鼠胃运动的影响

给药前先记录清醒大鼠胃运动曲线，待曲线稳定后，向 DVC 内注射不同浓度的 orexin-A。结果显示：与 NS 组相比，DVC 微量注射不同浓度 orexin-A，大鼠胃收缩幅度增加及收缩频率升高，随着药物浓度的增加，胃运动的改变增加($P<0.05$，图 1)。DVC 注射 orexin-A 和 SB334867 混合液时，orexin-A 对胃运动的作用减弱($P>0.01$，图 1)。DVC 单独注射 SB334867，大鼠胃运动无明显变化($P>0.05$，图 1)。

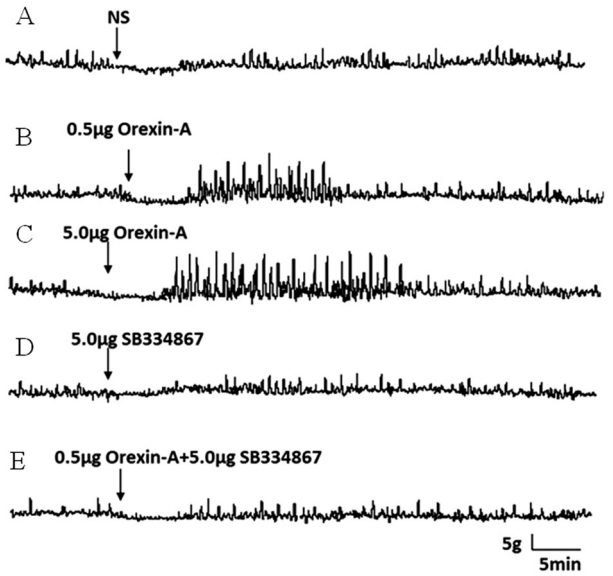

图 1 DVC 注射 orexin-A 对大鼠胃运动的影响

Fig.1 Effects of microinjection of orexin-A into DVC on the gastric motility of rat

2.2 DVC 注射 orexin-A 对大鼠胃液分泌的影响

与盐水组相比，DVC 注射不同浓度 orexin-A 的大鼠胃液及胃酸分泌增加($P<0.05$，表 1)，并且呈剂量依赖性。SB334867 可以消除 orexin-A 的作用 ($P>0.05$)。与 NS 对照组相比，DVC 单独注射 orexin-A 受体拮抗剂 SB334867，大鼠胃液及胃酸分泌无明显变化($P>0.05$，表 1)。

表 1 DVC 注射 orexin-A 对大鼠胃液和胃酸分泌的影响(n=6, $\bar{x}\pm s$)

Table 1 Effects of microinjection of orexin-A into DVC on the gastric juice and gastric acid secretion of rats

Group	gastric juice (mL/h)	gastric acid (μEq/h)
NS	0.72± 0.12	81.02± 9.12
0.5 μg orexin-A	1.48± 0.32*	107.62± 12.23*
5.0 μg orexin-A	1.93± 0.58**	155.79± 22.26**
SB334867	0.82± 0.21	78.45± 9.13
SB334867+orexin-A	0.93± 0.29$^{\#}$	85.62± 12.61$^{\#\#}$

Note: *$P<0.05$, **$P<0.01$, vs NS group, $^{\#}P<0.05$, $^{\#\#}P<0.01$, vs 0.5 μg orexin-A group.

3 讨论

下丘脑外侧区是一个重要的调控中心，主要参与调节食欲、进食、自主活动及胃肠功能[12,13]。Orexin-A 作为一种新型的神经肽，主要由下丘脑外侧区神经元分泌，在下丘脑穹窿周核也有分布[14,15]。研究表明 Orexin-A 在 LHA 发挥重要摄食调控作用[16]。Bülbül 等人曾报道侧脑室注射 orexin-A 可促进大鼠胃运动[5]。也有研究证明侧脑室注射 Orexin-A 可加速啮齿类动物的胃排空[17,18]，但抑制小鼠的胃肠运动[19]。中枢注射 Orexin-A 可调节大鼠非应激条件下的餐后胃运动[20]。有中枢内源性 Orexin-A 可通过迷走神经通路刺激胃的收缩 [21]。此外，中枢内 Orexin-A 在功能性胃肠病的病理生理过程中发挥重要作用[22,23]。有研究表明肠道组织中有 Orexin 的存在[24]，注射 Orexin-A 到下丘脑能激活迷走神经系统从而诱导胃酸分泌，但是腹腔内注射 Orexin-A 不能产生相同的作用[25]。迷走神经背核的 OX1 受体激活能促进迷走胰腺传出神经活动，从而刺激胰腺外分泌活动[26]。关节腔内注射 Orexin-A，正常饮食大鼠十二指肠的分泌增加，但是禁食大鼠不出现此类现象，这是由于胆碱能通路独立作用的原因[27]。

Orexin-A 可以调节胃肠蠕动，包括胃排空，胃消化间期的运动[28]，肠蠕动[29]，以及结肠蠕动[30]。不管是中枢注射还是外周注射，注射位置不同，Orexin 对胃运动的影响不用，其产生机制与乙酰胆碱和 NO 有关[31]。Orexin-A 对于应激产生的胃损伤有保护作用，例如抗应激，局部缺血 - 再灌注或乙醇诱导。本研究

结果显示:迷走神经复合体(DVC)微量注射 orexin-A 可显著影响胃运动以及胃液的分泌,但预先 DVC 给予 orexin-A 受体拮抗剂 SB334867 可显著阻断 orexin-A 该效应。因此,外源性 orexin-A 可通过作用于 DVC 内的 OX1R 促进大鼠胃运动。Krowicki 等曾证明在迷走背核 orexin-A 能增强大鼠的胃收缩[11]。本研究结果显示 orexin-A 可激活 DVC 内 OXR 神经元,通过迷走神经通路增强胃收缩。

迷走神经复合体是集感觉传入、整合、内脏传出于一体的内脏副交感神经的中枢,其中迷走神经背核是内脏运动核团,孤束核、迷走神经背核及极后区属于内脏感觉核团。孤束核和极后区接受来自腹腔脏器传入的感受信息,经整合和传递至大脑中枢,调控摄食。而迷走神经背核主要调控胃肠运动以及胃酸的分泌[32]。虽然受 orexin 神经末梢支配的迷走神经复合体的神经元类型还未知,但是 orexins 可能会改变迷走神经运动背核的活性,和 / 或调节孤束核神经元对胃肠道的刺激。刺激外侧核能够兴奋迷走神经背核神经元,并且增加迷走神经传出神经的活性[33,34]。因此,Orexins 对迷走神经活性的调控可以影响条件反射和 / 或胃肠道动力和消化液分泌。此外,孤束核神经元投射至外侧核后,孤束核转达的饱腹信号能调节 orexins 表达[35]。在后脑的迷走神经背核复合体中也发现了 orexin 阳性纤维,包括孤束核、迷走神经运动背核和极后区[36,37]。孤束核能传递与摄食有关[38,39]的肠道迷走神经传入信号。孤束核中有葡萄糖敏感性神经元,葡萄糖敏感性神经元能够对由血糖和肠道内食物变化引起的电生理活性做出应答[40,41]。迷走神经运动背核的神经元能调控胃肠动力和消化液分泌。迷走神经运动背核也参与胃肠道营养素消化吸收的起始阶段[42]。极后区与迷走神经背核复合体之间相互联系,是循环因子如肠蛋白和葡萄糖[43]传输到脑的重要室周器官。

虽然在关于能量平衡的研究中较多涉及下丘脑,但肠道也参与对摄食的调节。肠道内的食物在化学性和机械敏感性作用下,刺激一些调节蛋白释放,进一步调控肠动力和分泌物的释放[38,44]。这些调节蛋白也作为 " 饱腹感 " 的反馈信号来结束摄食[38,44,45]。禁食时,肠道内的饱腹感信号受到抑制,取而代之的是与 " 饥饿 " 相关的信号,这一信号可能因过低的葡萄糖血糖浓度而增强[38]。胃肠道壁的神经元组成肠神经系统,其含有的神经元数量与整个脊髓系统同样多[46],能够直接感知、整合和调节肠道内结构变化,进而参与能量代谢[46,47]。这是周围神经系统中唯一一个可以从根本上调节与肠道有关的反射活动的区域[47]。肠道内的微电路包含必需的主要传入神经元和中间神经元,这些神经元调节有关条件反射,如促进腺体分泌或肠蠕动。肠道内还有兴奋性和抑制性运动神经元,这些神经元能够支配胃肠道平滑肌和腺体。最近有报道指出,肠道内的神经元和内分泌细胞表现出与 orexin 相似的免疫反应性[48]。此外,orexins 能够调节促分泌神经元的电生理和突触传入,并且刺激结肠运动。有证据指出,在禁食阶段 orexins 分泌增多,这也表明了这些细胞对食物的机能反应。这些观察结果表明,orexins 存在于中枢神经系统和肠神经系统,并发挥一定作用,但是有关肽能的脑肠轴调控摄食和能量平衡的研究有待进一步研究。

近来,有研究显示肠道能够分泌 orexins。在肠神经系统内发现了许多不同类型的神经递质,如脑内主要的兴奋性神经递质 --- 谷氨酸盐[49,50]。肠神经元和肠上皮内分泌细胞包含大部分的下丘脑促食性神经肽和厌食性神经肽,如 NPY、ghrelin、甘丙肽和可卡因苯丙胺调节转录因子[51]。而且,与下丘脑一样的是,肠神经系统内的神经元也具有葡萄糖敏感性,并由脂肪细胞分泌的瘦素来调节[52]。虽然这些因子在调节摄食时缺乏一定的生理性关联,但许多因子能够像外周因子一样调节能量平衡。

综上所述,DVC 微量注射 orexin-A 可调控大鼠胃运动,Orexin-A 作为一种调节性神经肽,可增强大鼠胃运动,刺激胃酸分泌,orexin-A 有望成为一种新型药剂,可能用于治疗肥胖症等代谢疾病。

参 考 文 献(References)

[1] Terrill SJ, Hyde KM, Kay KE, et al. Ventral tegmental area orexin 1 receptors promote palatable food intake and oppose postingestive negative feedback[J]. Am J Physiol Regul Integr Comp Physiol, 2016, 311(3): 592-599

[2] Li SB, Giardino WJ, de Lecea L. Hypocretins and Arousal [J]. Curr Top Behav Neurosci, 2016, 15(7): 66-72

[3] Brown JA, Woodworth HL, Leinninger GM. To ingest or rest? Specialized roles of lateral hypothalamic area neurons in coordinating energy balance[J]. Front Syst Neurosci, 2015, 18(9): 1-9

[4] Apergis-Schoute J, Iordanidou P, Faure C, et al. Optogenetic evidence for inhibitory signaling from orexin to MCH neurons via local microcircuits[J]. J Neurosci, 2015, 35(14): 5435-5441

[5] Nozu T1, Tuchiya Y, Kumei S, et al. Endogenous orexin-A in the brain mediates 2-deoxy-D-glucose-induced stimulation of gastric motility in freely moving conscious rats. [J]. J Gastroenterol, 2012, 47 (4): 404-411

[6] Bigley AB, Spielmann G, Agha N, et al. Dichotomous effects of latent CMV infection on the phenotype and functional properties of $CD8^+$ T-cells and NK-cells[J]. Cell Immunol, 2016, 300: 26-32

[7] Li J, Hu Z, de Lecea L. The hypocretins/orexins: integrators of multiple physiological functions[J]. Br J Pharmacol, 2014, 171(2): 332-350

[8] Parekh PK, McClung CA. Circadian mechanisms underlying reward-related neurophysiology and synaptic plasticity[J]. Front Psychiatry, 2016, 6(4): 187-198

[9] Ertaylan G, Okawa S, Schwamborn JC, et al. Gene regulatory network analysis reveals differences in site-specific cell fate determination in mammalian brain[J]. Front Cell Neurosci, 2014, 8(6): 437-464

[10] Namkoong C, Toshinai K, Waise TM, et al. NERP-2 regulates gastric acid secretion and gastric emptying via the orexin pathway [J]. Biochem. Biophys Res Commun, 2017, 485 (2): 409-413

[11] Nozu T1, Tuchiya Y, Kumei S, et al. Endogenous orexin-A in the brain mediates 2-deoxy-D-glucose-induced stimulation of gastric motility in freely moving conscious rats [J]. J Gastroenterol, 2012, 47 (4): 404-411

[12] Sheng Z, Santiago A M, Thomas M P, et al. Metabolic regulation of lateral hypothalamic glucose-inhibited orexin neurons may influence midbrain reward neurocircuitry [J]. Mol Cell Neurosci, 2014, 62(16): 30-41

[13] Goforth PB, Leinninger GM, Patterson CM, et al. Leptin acts via lateral hypothalamic area neurotensin neurons to inhibit orexin neurons by multiple GABA-independent mechanisms[J]. J Neurosci, 2014, 34

(8): 11405-11415

[14] Goforth PB, Leinninger GM, Patterson CM, et al. Leptin acts via lateral hypothalamic area neurotensin neurons to inhibit orexin neurons by multiple GABA-independent mechanisms[J]. J Neurosci, 2014, 34 (34): 11405-11415

[15] Anderson RI, Becker HC, Adams BL, et al. Orexin-1 and orexin-2 receptor antagonists reduce ethanol self-administration in high drinking rodent models[J]. Front Neurosci, 2014, 8(2): 1-9

[16] Tabuchi S, Tsunematsu T, Black SW, et al. Conditional ablation of orexin/hypocretin neurons: a new mouse model for the study of narcolepsy and orexin system function [J]. J. Neurosci, 2014, 34(14): 6495-6509

[17] Steiner MA, Sciarretta C, Brisbare-Roch C, et al. Examining the role of endogenous orexins in hypothalamus-pituitary-adrenal axis endocrine function using transient dual orexin receptor antagonism in the rat[J]. Psychoneuroendocrinology, 2013, 38(4): 560-571

[18] Bülbül M, Tan R, Gemici B, et al. Endogenous orexin-A modulates gastric motility by peripheral mechanisms in rats [J]. Peptides, 2011, 31(10): 1099-1108

[19] Bae JH, Im SS, Song DK, et al. Orexin A regulates plasma insulin and leptin levels in a time-dependent manner following a glucose load in mice[J]. Diabetologia, 2015, 58(7): 1542-1550

[20] Sun S, Xu L, Sun X, et al. Orexin-A affects gastric distention sensitive neurons in the hippocampus and gastric motility and regulation by the perifornical area in rats[J]. Neurosci Res, 2016, 110(17): 59-67

[21] Nozu T, Tuchiya Y, Kumei S, et al. Endogenous orexin-A in the brain mediates 2-deoxy-D-glucose-induced stimulation of gastric motility in freely moving conscious rats [J]. J Gastroenterol, 2012, 47 (6): 404-411

[22] Okumura T, Nozu T. Antinociceptive action against colonic distension by brain orexin in conscious rats [J]. Brain Res, 2015, 1598(1): 12-17

[23] Chaleek N, Kermani M, Eliassi A, et al. Effects of orexin and glucose microinjected into the hypothalamic paraventricular nucleus on gastric acid secretion in conscious rats [J]. Neurogastroenterol Motil, 2012, 24(5): e94-e102

[24] Blais A, Drouin G, Chaumontet C, et al. Impact of Orexin-A Treatment on Food Intake, Energy Metabolism and Body Weight in Mice [J]. PLoS One, 2017, 12(1): e0169908

[25] Kermani M, Eliassi A. Gastric acid secretion induced by paraventricular nucleus microinjection of orexin A is mediated through activation of neuropeptide Yergic system [J]. Neuroscience, 2012, 226: 81-88

[26] Arafat AM, Kaczmarek P, Skrzypski M, et al. Glucagon regulates orexin A secretion in humans and rodents [J]. Diabetologia, 2014, 57 (10): 2108-2116

[27] Gao HR, Zhuang QX, Zhang YX, et al. Orexin Directly Enhances the Excitability of Globus Pallidus Internus Neurons in Rat by Co-activating OX1 and OX2 Receptors[J]. Neurosci Bull, 2017, 18(3): 28-33

[28] Bulbul M, Babygirija R, Ludwig K, et al. Central orexin-A increases gastric motility in rats[J]. Peptides, 2015, 31(9): 2118-2122

[29] Satoh Y, Okishio Y, Azuma YT, et al. Orexin A affects ascending contraction depending on downstream cholinergic neurons and descending relaxation through independent pathways in mouse jejunum [J]. Neuropharmacology, 2012, 51(3): 466-473

[30] Nozu T, Kumei S, Takakusaki K, et al. Central orexin-A increases colonic motility in conscious rats [J]. Neuroscience letters, 2012, 498 (3): 143-146

[31] Arcamone N, D'Angelo L, de Girolamo P, et al.Orexin and orexin receptor like peptides in the gastroenteric tract of Gallus domesticus: An immunohistochemical survey on presence and distribution[J]. Res Vet Sci, 2014, 96(2): 234-240

[32] Hurley SW, Johnson AK. The role of the lateral hypothalamus and orexin in ingestive behavior: a model for the translation of past experience and sensed deficits into motivated behaviors [J]. Front Syst Neurosci, 2014, 8(12): 216-237

[33] Nishimura H, Oomura Y. Effects of hypothalamic stimulation on activity of dorsomedial medullar neurons that respond to subdiaphragmatic vagal stimulation[J]. J Neurophysiol, 1987, 58(5): 655-675

[34] Yahagi N. Hepatic Control of Energy Metabolism via the Autonomic Nervous System[J]. J Atheroscler Thromb, 2017, 24(1): 14-18

[35] Corson JA, Bradley RM. Physiological and anatomical properties of intramedullary projection neurons in rat rostral nucleus of the solitary tract[J]. J Neurophysiol, 2013, 110(5): 1130-1143

[36] Peyron C, Tighe DK, van den Pol AN, et al. Neurons containing hypocretin (orexin) project to multiple neuronal systems [J]. J Neurosci, 2012, 18(23): 9996-10015

[37] Willie JT, Chemelli RM, Sinton CM, et al. To eat or to sleep? Orexin in the regulation of feeding and wakefulness [J]. Annu Rev Neurosci, 2013, 24(5): 429-458

[38] Bray GA. Afferent signals regulating food intake[J]. Proc Nutr, 2000, 59(3): 373-384

[39] Schwartz GJ. The role of gastrointestinal vagal afferents in the control of food intake: current prospects[J]. Nutrition, 2000, 16(10): 866-873

[40] McDougal DH, Hermann GE, Rogers RC. Astrocytes in the nucleus of the solitary tract are activated by low glucose or glucoprivation: evidence for glial involvement in glucose homeostasis [J]. Front Neurosci, 2013, 7(10): 249-251

[41] Yettefti K, Orsini JC, Perrin J. Characteristics of glycemiasensitive neurons in the nucleus tractus solitarii: possible involvement in nutritional regulation[J]. Physiol Behav, 1997, 61(1): 93-100

[42] Berthoud HR, Powley TL. Identification of vagal preganglionics that mediate cephalic phase insulin response [J]. Am J Physiol, 1990, 258 (2 Pt 2): R523-530

[43] Whitcomb DC, Taylor IL. A new twist in the brain-gut axis [J]. Am J Med Sci, 1992, 304(5): 334-338

[44] Furness JB, Kunze WAA, Clerc N. Nutrient tasting and signaling mechanisms in the gut. II. The intestine as a sensory organ: neural, endocrine, and immune responses [J]. Am J Physiol Gastrointest Liver Physiol, 1999, 277 (5 Pt 1): G922-G928

[45] Moran T. Cholecystokinin and satiety: current perspectives[J]. Nutrition, 2000, 16(10): 858-865

[46] Furness JB, Costa M. The enteric nervous system [J]. New York: Churchill Livingstone, 1987, 44(3): 103-107 (下转第 1610 页)

ease severity of severe fever with thrombocytopenia syndrome [J]. J Infect Dis, 2012, 206(7): 1085-1094

[10] Peng C, Wang H, Zhang W, et a1. Decreased monocyte subsets and TLR4-mediated functions in patients with acute severe fever with thrombocytopenia syndrome (SFTS) [J]. Int J Infect Dis, 2016, 43: 37-42

[11] 韩亚萍,董莉,孔练花,等.病毒载量和细胞因子在发热伴血小板减少综合征致病机制中的作用 [J]. 中华传染病杂志, 2014, (9): 538-544
Han Ya-ping, Dong Li, Kong Lian-hua, et al. Viral load and cytokines in the pathogenesis of severe fever with thrombocytopenia syndrome [J]. Chinese Journal of Infectious Diseases, 2014, (9): 538-544

[12] 何程程,李阿茜,刘林,等.发热伴血小板减少综合征布尼亚病毒细胞嗜性研究[J].中华实验和临床病毒学杂志, 2014, 28(1): 10-13
He Cheng-cheng, Li A-qian, Liu Lin, et al. The susceptibility of culture cells to severe fever with thrombocytopenia syndrome virus [J]. Chinese Journal of Experimental and Clinical Virology, 2014, 28(1): 10-13

[13] 杜燕华,黄学勇,邓文斌,等.新布尼亚病毒在非洲绿猴肾细胞中的培养与分离鉴定[J].中华预防医学杂志, 2012, 46(2): 169-172
Du Yan-hua, Huang Xue-yong, Deng Wen-bin, et al. Culture, isolation and identification of new bunyavirus in African green monkey kidney (Vero) cells[J]. Chinese Journal of Preventive Medicine, 2012, 46(2): 169-172

[14] Xu Chen, Haiyan Ye, Shilin Li, et al. Severe fever with thrombocytopenia syndrome virus inhibits exogenous Type I IFN signaling pathway through its NSs in vitro[J]. PLoS One, 2017, 12(2): e0172744

[15] Lu X, Wang L, Bai D, et al. Establishment of national reference for bunyavirus nucleic acid detection kits for diagnosis of SFTS virus[J]. Virol J, 2017, 14(1): 32

[16] Chaudhary V, Zhang S, Yuen KS, et al. Suppression of type I and type III IFN signalling by NSs protein of severe fever with thrombocytopenia syndrome virus through inhibition of STAT1 phosphorylation and activation[J]. J Gen Virol, 2015, 96(11): 3204-3211

[17] Jiao Y, Zeng X, Guo X, et al. Preparation and evaluation of recombinant severe fever with thrombocytopenia syndrome virus nucleocapsid protein for detection of total antibodies in human and animal sera by double-antigen sandwich enzyme-linked immunosorbent assay[J]. J Clin Microbiol, 2012, 50(2): 372-377

[18] Rang A, Heider H, Ulrich R, et a1. A novel method for cloning of non-cytolytic viruses[J]. J Virol Methods, 2006, 135(1): 26-31

[19] Handke W, Oelschlegel R, Franke R, et a1. Hantaan virus triggers TLR3-dependent innate immune responses [J]. J Immunol, 2009, 182 (5): 2849-2858

[20] Yu HT, Jiang H, Zhang Y, Nan XP, et a1. Hantaan virus triggers TLR4-dependent innate immune responses [J]. Viral Immunol, 2012, 25(5): 387-393

[21] Huang HI, Chio CC, Lin JY, et al. Inhibition of EV71 by curcumin in intestinal epithelial cells[J]. PLoS One, 2018, 13(1): e0191617

[22] Schiavoni I, Scagnolari C, Horenstein AL, et al. CD38 modulates respiratory syncytial virus-driven proinflammatory processes in human monocyte-derived dendritic cells[J]. Immunology, 2017

[23] Wong HH, Fung TS, Fang S, et al. Accessory proteins 8b and 8ab of severe acute respiratory syndrome coronavirus suppress the interferon signaling pathway by mediating ubiquitin-dependent rapid degradation of interferon regulatory factor 3[J]. Virology, 2017, 515: 165-175

[24] 蒋虹,乔红伟,丛喆,等.SARS-CoV 细胞空斑试验[J].中国比较医学杂志, 2009, 19(8): 65-66
Jiang Hong, Qiao Hong-wei, Cong Zhe, et al. Plaque Assay in SARS-CoV Titration [J]. Chinese Journal of Comparative Medicine, 2009, 19 (8): 65-66

[25] De Wilde AH, Zevenhoven-Dobbe JC, Beugeling C, et al. Coronaviruses and arteriviruses display striking differences in their cyclophilin A-dependence during replication in cell culture[J]. Virology, 2017

[26] De Wilde AH, Raj VS, Oudshoorn D, et al. MERS-coronavirus replication induces severe in vitro cytopathology and is strongly inhibited by cyclosporin A or interferon-α treatment [J]. J Gen Virol, 2013, 94 (Pt 8): 1749-1760

[27] Taniguchi S, Fukuma A, Tani H, et al. A neutralization assay with a severe fever with thrombocytopenia syndrome virus strain that makes plaques in inoculated cells[J]. J Virol Methods, 2017, 244: 4-10

(上接第 1636 页)

[47] Roy-Carson S, Natukunda K, Chou HC et al. Defining the transcriptomic landscape of the developing enteric nervous system and its cellular environment[J]. BMC Genomics, 2017, 18(1): 290-293

[48] Goforth PB, Myers MG Jr. Roles for Orexin/Hypocretin in the Control of Energy Balance and Metabolism[J]. Curr Top Behav Neurosci, 2016, 17(3): 134-138

[49] Liu MT, Rothstein JD, Gershon MD, et al. Glutamatergic enteric neurons[J]. J Neurosci, 1997, 17(12): 4764-4784

[50] Gasic G. Systems and molecular genetic approaches converge to tackle learning and memory[J]. Neuron, 1995, 15(3): 507-512

[51] Clark JT, Kalra PS, Crowley WR, et al. Neuropeptide Y, and human pancreatic polypeptide stimulate feeding behavior in rats [J]. Endocrinology, 1984, 115(1): 427-429

[52] Liu M-T, Seino S, Kirchgessner AL. Identification and characterization of glucoresponsive neurons in the enteric nervous system [J]. J Neurosci, 1999, 19(23): 10305-10317