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Orexin 在隔核对大鼠胃传入信息的调控 *

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摘要 目的：研究 orexin 在隔核对大鼠胃传入信息的调控作用。**方法：**选取健康成年雄性 Wistar 大鼠 138 只(体质量 250-300 g)，记录神经元放电活动，鉴定隔核胃牵张(GD)敏感性神经元；隔核微量注射 orexin-A 或 orexin-A 受体拮抗剂 SB334867，观察隔核 GD 敏感性神经元放电活动变化；隔核微量注射不同浓度的 orexin-A，观察大鼠胃运动的变化。**结果：**隔核微量注射 orexin-A 的大鼠胃运动幅度和频率显著增加，并呈剂量依赖关系(P<0.05-0.01)，微量注射 SB-334867 可完全阻断 orexin-A 对胃运动的影响。隔核微量注射 orexin-A 后，有 36 个 GD-E 神经元兴奋 (P<0.01)，16 个 GD-I 神经元抑制。Orexin-A 受体拮抗剂 SB334867 可完全阻断 orexin-A 对 GD 敏感神经元的作用。**结论：**隔核注射 orexin 能促进大鼠胃运动，并影响胃牵张敏感神经元的放电活动。

关键词：Orexin-A；隔核；胃传入信息；胃运动

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Regulation of Orexin on the Gastric Afferent Information in Rats*

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ABSTRACT Objective: To study the regulation of orexin on the gastric afferent information in the septal nuclei of rats. **Methods:** 138 adult male Wistar rats weighed 250-300 g were selected, extracellular discharges of single unit neuron in the septal nuclei were used to identify the gastric distension(GD) sensitive neurons. Microinjection of orexin-A or orexin-A receptor antagonist SB334867 into septal nuclei was performed to explore the changes of GD sensitive neurons in the septal nuclei. The effects of different concentrations of orexin-A on the gastric motility of rats were observed. **Results:** The gastric motility experiments showed that administration of orexin-A in the septal nuclei could significantly increase the amplitude and frequency of gastric motility in a dose-dependent manner (P<0.05-0.01). Microinjection of SB-334867 could completely block the effect of orexin-A on the gastric motility. After the septal nuclei Microinjection of orexin-A, there were 36 GD excitatory (GD-E) neurons and 16 GD inhibitory (GD-I) neurons. The effects induced by orexin-A on GD sensitive neurons were completely abolished with administration of SB-334867. **Conclusion:** Injection of orexin into the septal nuclei could promote the gastric motility in rats and also change the discharge activity of gastric distention (GD) sensitive neurons.

Key words: Orexin-A; Septal nucleus; Gastric afferent information; Gastric motility

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前言

Orexin-A 是一种兴奋性神经肽，对食欲、兴奋性、警觉性、奖励 - 成瘾行为、神经内分泌稳态和代谢与能量消耗之间的平衡均有调节作用[1,2]。研究表明中枢和外周注射 orexin-A 可调节胃自发 III 期样收缩，增强胃动力，促进大鼠胃排空[3]。此外，侧脑室注射 orexin-A 可剂量依赖性增加大鼠摄食量以及胃动力[4-6]。近几年有研究显示隔核(Sep)同样也参与摄食、胃运动、能量代谢的调节，并在其中扮演着重要的角色。形态学研究显示隔核与下丘脑室旁核(PVN)、弓状核(ARC)、视上核(SON)、外侧核(LHA)、脑干孤束核(NTS)、迷走神经背核(DMV)、延髓等脑区之间均存在着复杂的神经纤维，这些神经核团能对内脏传入信号和传出信号进行整合和处理，从而参与摄食调控。已有研究证实隔核存在大量 orexin 能纤维投射和 orexin 受体[7]，但隔核在 orexin 能系统中对大鼠胃运动的作用尚无深入研究。神经纤维的广泛投射提示中枢 orexin-A 可调控多种功能，包括胃运动和能量平衡[8,9]。本研究旨在探讨隔核注射 orexin 对胃牵张敏感神经元和胃运动的影响。

1 材料和方法

1.1 实验动物

成年雄性 Wistar 大鼠(n=138)，体质量 250-300 g，所有大鼠

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均在室温(25± 2 ℃)、昼夜循环光照(08:00 至 20:00)下饲养,给予实验室标准饮食,不限制摄食和饮水。所有动物实验均严格按《青岛大学实验动物保护和使用管理办法》执行。

1.2 电生理实验

大鼠(n=90)禁食 18 h,10 %水合氯醛腹腔麻醉(0.3 mL/100 g),必要时适当增补麻醉剂。无菌条件下,麻醉大鼠行腹部正中纵行切口,打开腹腔,暴露胃组织,在胃底部作 1 cm 的切口,经切口放入薄软胶气囊,与 5 mL 注射器连接,,以 0.5 mL/s 的速度向气囊注入 37 ℃温生理盐水(3-5 mL)扩张胃壁,以刺激胃壁机械感受器,鉴别胃扩张敏感性神经元,胃扩张状态需保持 10-30 s。

腹部手术后将大鼠固定于脑立体定位仪,暴露颅骨,海马(前囟后 3.30 mm, 旁开 2.0 mm,颅骨下 3.0 mm)处牙科钻开颅骨,剥除脑膜暴露脑实质。四管玻璃微电极(电极尖端直径 3-10 mm,电极阻抗 5-15 MΩ),用于微量注射和细胞外电生理记录,用液压推进器将玻璃微电极送至海马。四管玻璃微电极分别灌注 20 g/L 滂胺天蓝、15 nmol/L orexin-A、25 nmol/L SB-334867 以及 9 g/L 的生理盐水,滂胺天蓝用于标记电极放入位置。将电极放入隔核,记录并保存神经元放电活动信号,待神经元放电活动稳定之后,向置入胃内的薄软胶气囊注入温生理盐水 3-5 mL,10-30 s 后抽出生理盐水,观察神经元放电活动的变化。神经元放电频率变化超出 20 %的神经元定义为 GD 敏感性神经元,放电频率增加的神经元是胃牵张兴奋型神经元(GD-E),放电频率降低的神经元是胃牵张抑制型神经元(GD-E)[10]。

1.3 胃运动实验

48 只大鼠术前禁食 18 h,自由饮水。大鼠腹腔注射 10 %水合氯醛 0.3 mL/100 g 进行麻醉,麻醉后固定于脑立体定位仪上,根据大鼠脑图谱 Paxinos-Watson,隔核放置套管(前囟后 0.7 mm, 旁开 0.5 mm, 颅骨下 5.5 mm)[11]。套管植入后,将大鼠仰卧于操作台,75 %酒精消毒,行纵形切口打开腹腔,暴露胃部。将应力传感器在距幽门 0.5 cm 处沿环形肌方向缝贴于胃窦浆膜面,导线经皮下固定于颈部,露出 2-3 cm,缝合腹部切口。术后给予动物正常饮食 3 天。

实验时,大鼠先置于实验区特制鼠笼内 30 min 以适应实验环境,从而避免环境因素对记录的影响。胃运动记录前禁食 18 h,记录期间大鼠可自由活动,自由饮水,大鼠清醒状态下将应力传感器与桥式放大器相连,观察并记录大鼠胃收缩幅度及胃收缩频率。在给药前各组稳定记录胃基线运动 30 min,之后各组分别通过颅内置管缓慢给药,对照组注射等体积生理盐水。给药后记录 60 min,观察给药前后胃收缩频率和幅度的变化,并计算变化率。每只大鼠每天记录 1-2 h,至少持续 2 天。

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

大鼠经心脏灌注固定,快速断头取脑,50 μm 系列冠状切片,参照大鼠脑图谱检测置入套管尖端定位,定位不准确者弃去不用。

1.4 统计学分析

所有数据使用 SPSS 18.0 和 PPMS 1.5 软件分析,所有数据均以($\bar{X}$± SD)表示,多样本均数比较采用单因素方差分析,两组间样本均数比较采用 t 检验,P＜0.05 为差异有统计学意义。

2 结果

2.1 隔核微量注射 orexin-A 对大鼠胃运动的影响

如表 1 所示,与生理盐水对照组相比,隔核微量注射 orexin-A 的大鼠胃运动幅度和频率均显著增加,并呈剂量依赖关系(P<0.05-0.01)。微量注射 orexin-A 10-15 分钟后,与 0.05 μg 0.5 μL orexin-A 组相比,0.5 μg 或 5.0 μg 0.5 μL orexin-A 组的大鼠胃运动收缩频率显著增加 (P<0.01)。隔核给予 0.5 μg orexin-A 与 5.0 μg SB-334867-A 的混合液 0.5 μL,orexin-A 的促胃运动效应消失(P>0.05)。隔核单独注射生理盐水或 SB-334867 的大鼠胃运动幅度无显著变化(P>0.05)。

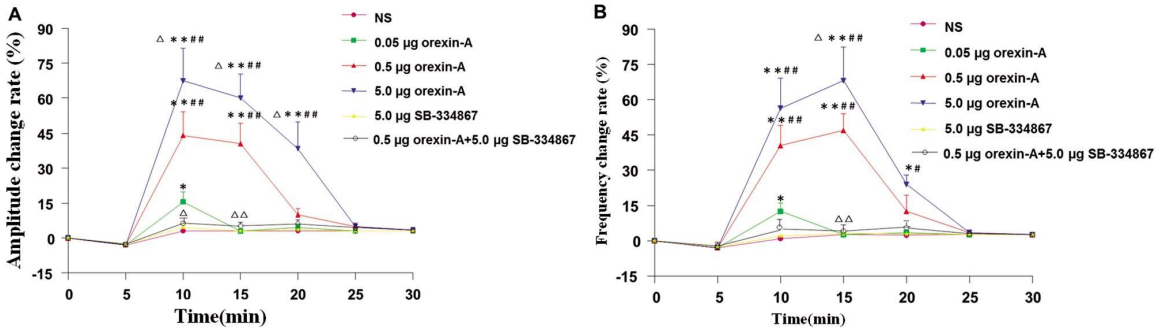

图 1 隔核微量注射 orexin-A 对大鼠胃运动的影响

A:胃收缩幅度;B:胃收缩频率

*P<0.05,**P<0.01,与 NS 组相比;#P<0.05,##P<0.01,与 0.05μg orexin-A 组相比;△ P< 0.05,△△ P< 0.01 与 0.5 μg orexin-A 组相比

Fig.1 Effect of microinjection of orexin-A into septal nucleus on the gastric motility of rats

A: gastric contraction amplitude; B: gastric contraction frequency

*P<0.05, **P<0.01, vs NS group; #P<0.05, ##P<0.01, vs 0.05 μg orexin-A group; △ P<0.05, △△ P<0.01 vs 0.5 μg orexin-A group

2.2 Orexin-A 对隔核 GD 神经元放电活动的影响

通过对 90 只大鼠隔核放电活动的记录,共有 173 个神经元自发放电,其中 GD 神经元的有 109 个(109/173,63.0 %)。胃扩张刺激后,109 个 GD 神经元中有 57 个为 GD 兴奋性(GD-E)神经元,52 个为 GD 抑制性(GD-I)神经元。经微电极微量注射 orexin-A 后,隔核 57 个 GD-E 神经元中有 36 个 GD-E 神经元

(36/57,63.1 %) 兴奋，其放电频率从 7.8± 2.1 Hz 增加到 9.4± 1.3 Hz (P<0.01;表 1、图 2),有 16 个 GD-E 神经元(16/57,28.0 %) 放电被抑制 (放电频率从 8.1± 1.7 Hz 下降到 4.9± 1.2Hz (P<0.01,表 1),其余 5 个 GD-E 神经元(5/57,8.9 %)没有明显变化(P>0.05,表 1)。Orexin-A 可兴奋神经元,给予 orexin 受体拮抗剂 SB-334867 后再给予 orexin-A,orexin-A 兴奋效应可被完全阻断(图 2A)。而隔核微量注射 SB-334867 对 GD-E 神经元的放电活动无显著影响。

隔核 52 个 GD-I 神经元经微电极微量注射 orexin-A 后,其中有 28 个 GD-I 神经元(28/52,53.8%)放电频率从 4.6 ± 1.4 Hz 增加到 7.1 ± 1.8 Hz (P<0.01,表 1、图 2B),16 个 GD-I 神经元(16/52,30.7 %)放电呈现抑制效应(放电频率从 4.6± 1.1 Hz 下降到 2.9± 0.8 Hz(P<0.01,表 1),8 个 GD-I 神经元(8/52,15.5 %)无显著反应(P>0.05,表 1)。给予 orexin 受体拮抗剂 SB-334867 后再给予 orexin-A,orexin-A 的兴奋效应可被完全阻断 (图 2B);隔核微量注射 SB-334867 对 GD-I 神经元的放电活动无显著影响。

表 1 Orexin-A **对隔核** GD **神经元放电活动的影响**($\bar{x}$± s)

Table 1 Effects of Orexin-A on the activity of GD neurons in septal nucleus ($\bar{x}$± s)

Neurons	Frenquency(Hz)		Numbers		
	Before orexin-A	After orexin-A	Excited	Inhibited	Insensitive
GD-E	7.8± 2.1	9.4± 1.3**	36 (63.1 %)	16(28.0 %)	5 (8.9%)
GD-I	4.6 ± 1.4	7.1 ± 1.8**	28(53.8%)	16(30.7 %)	8 (15.5 %)

Note: **P<0.01, vs. before orexin-A.

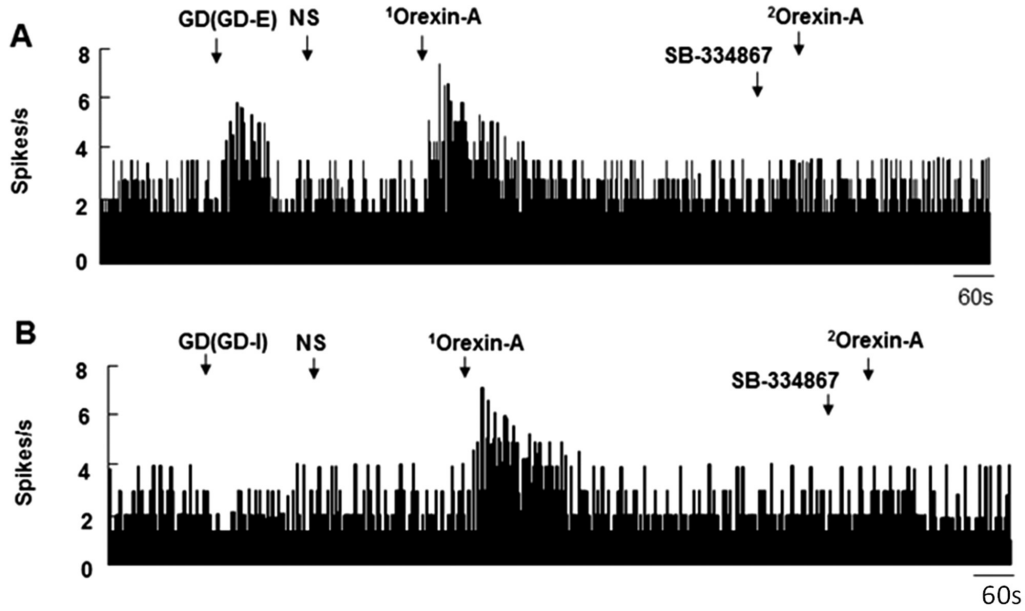

图 2 Orexin-A **对隔核** GD **神经元放电活动的影响。**A:GD-E **神经元**; B:GD-I **神经元。**

Fig. 2 Effect of Orexin-A on the activity of GD neurons in septal nucleus. A: GD-E neuron; B:GD-I neuron.

3 讨论

本研究通过向胃灌注生理盐水扩张胃模拟进食过程中胃的充盈状态,胃充盈后胃壁受刺激,胃壁上的胃牵张感受器将胃充盈信号传递至中枢神经系统,引起中枢与摄食有关的核团内神经元放电频率的改变,产生兴奋或抑制效应。大鼠隔核存在 GD 神经元，隔核微量注射 orexin-A 的大鼠 GD-E 和 GD-I 神经元放电频率显著增加,提示 orexin-A 可增加隔核中胃肠传入相关神经元的兴奋性，在隔核预先微量注射选择性 OX1 受体拮抗剂 SB-334867,orexin-A 诱导的 GD-E 和 GD-I 神经元兴奋效应可完全被阻断，提示 orexin-A 该效应可能是通过 OX1 受体而介导的。此外,隔核微量注射 orexin-A 可使大鼠胃运动显著增强,且该效应呈剂量依赖性增加,提示 orexin-A 在隔核参与胃运动调控。

下丘脑公被认为可通过多种外周信号和神经通路参与植物神经功能活动调控中心 [12]。下丘脑室旁核 (PVN)、弓状核 (ARC)、下丘脑腹内侧核(VMH)和穹窿周区(PeF)均参与摄食行为的调控。隔核是大脑边缘系统重要组成部分,参与学习和记忆相关行为调控[12]。有研究表明下丘脑和低位脑干活动的调节取决于与边缘系统的其他领域的密切连接[14]。已有研究显示隔核有许多胃肠功能调控神经肽及其受体表达,如 orexin-A 及其受体[15]、胃动素[16]、生长素[17]、生长素受体[18]或 nesfatin-1 等[19]。有研究证实隔核在介导中枢 orexin-A 的作用中非常重要[20],PCR [21]、Western blot[22]、免疫组织化学[14]以及免疫印迹研究[23]均显示隔核内表达 orexin-A 受体(OX1R)。隔核神经元可通过胃迷走神经和小脑传出通路来整合内脏和躯体信号传导[14],参与能量平衡和胃肠功能调控[24]。本研究结果显示隔核注射 orexin-A 可增加隔核内胃牵张敏感神经元放电频率，且同时胃运动加强，

提示隔核也可能是 orexin-A 参与胃运动调节重要功能区之一。但 orexin-A 是直接还是间接通过兴奋 GD 敏感性神经元促进胃运动尚无定论,还需进行进一步的研究。

orexin 受体在脑组织中广泛分布,如在蓝斑核(LC)、脑桥核(Pn)、伏隔核(NAc)、隔核(Sep)、中缝背核(Rdn)、下丘脑、中脑和网状结构等都有 orexin 受体的分布,因此 orexin 具有多种生物效应[25]。Orexins 的功能并不仅限于增食,其还在能量代谢、内分泌、睡眠 - 觉醒、循环和维持觉醒等生理过程中起重要调控作用。由于 orexin-A 在摄食行为和代谢方面的作用,其作为脑肠肽以得到越来越多的关注[21]。有研究显示 orexin-A 是胃排空和胃肠运动强有力的兴奋剂,可通过迷走神经传入终端的 orexin-A 受体发挥作用[26]。此外,迷走神经动核微量注射 orexin-A 后可促进胃收缩,中枢或外周注射 orexin-A 均能够刺激大鼠胃肠蠕动,促进胃酸分泌,预先注射阿托品或双侧颈迷走神经切断可阻断 orexin-A 对胃肠蠕动和胃酸分泌的促进作用[27]。同时,侧脑室注射 orexin-A 可促进大鼠摄食,其作用效果与黑色素凝集素(MCH)类似,但是弱于神经肽 Y(NPY)的作用[28]。

综上所述,可能参与胃传入信息和胃运动调控,Orexin-A 的该效应可能通过 OX1R 信号通路介导。因此,orexin-A 有望作为胃动力药,用于糖尿病性胃轻瘫或腹部手术后胃肠梗阻引起的胃动力减弱治疗[29,30]。

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