读书报告

汇报人：胡俊仪

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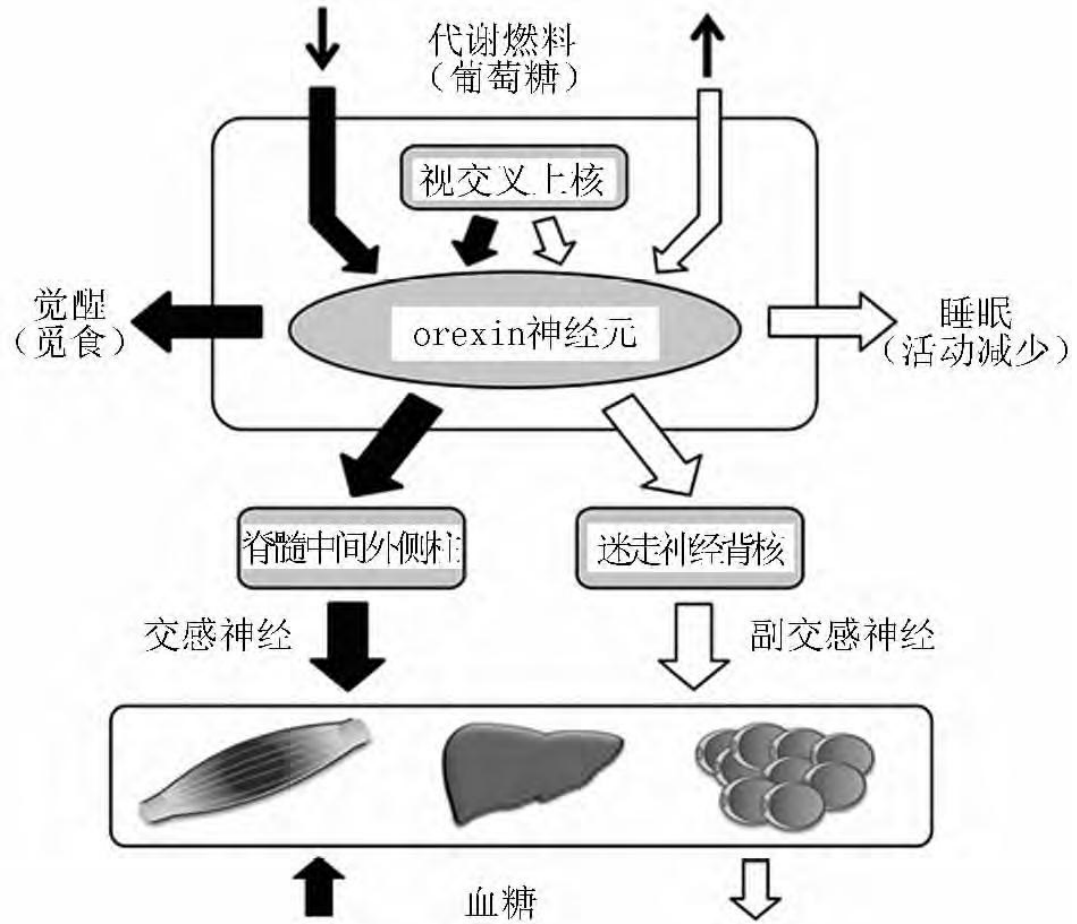
Orexin 的作用

Orexin是由外侧下丘脑神经元产生的一对兴奋性神经肽的合称。

近年研究发现, Orexins作用范围广泛, 不仅可促进食欲、增强能量代谢, 还可影响摄食、**能量平衡**, 睡眠/觉醒、呼吸、脑部创伤的并发症、学习与记忆、食物与药物成瘾、应激、胃肠道功能等。

Orexin 的作用



食欲素与血糖稳态双重调节

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A JOURNAL OF THE AMERICAN DIABETES ASSOCIATION

ORIGINAL ARTICLE

A Major Role for Perifornical Orexin Neurons in the Control of Glucose Metabolism in Rats

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下丘脑食欲素神经元在调控大鼠葡萄糖代谢中的主要作用

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研究目的

OBJECTIVE: The hypothalamic neuropeptide orexin influences (feeding) behavior as well as energy metabolism. Administration of exogenous orexin-A into the brain has been shown to increase both food intake and blood glucose levels. In the present study, we investigated the role of endogenous hypothalamic orexin release in glucose homeostasis in rats.

食欲素神经元激活

EGP(内源葡萄糖产生）的影响

研究材料

实验动物

雄性Wistar鼠体(300-350克)，放置在笼子（25-25- 35cm）中饲养，提供水和常规食品,12 h光 / 12 h暗周期 温度21－23℃。

Chemicals

[6,6-$^{2}H_2$]glucose， 神经元激活剂 (BIC)，Orexin-A，Orexin受体抑制剂，麻醉剂（Hypnorm，Dormicum）.

实验方法

研究设计

激活食欲素神经元是否对葡萄糖代谢产生影响

BIC激活

Orexin-A 定性、定量分析

血糖，EGP,Insulin

验证该神经元的激活是否通过Orexin-A影响糖代谢

Orexin-R抑制剂

注射Orexin-A

血糖，EGP,Insulin

肝脏去神经支配对内源葡萄糖产生的影响

交感神经，副交感，假去神经

血糖，EGP,Insulin

神经元食欲素对胰岛素及胰岛素抵抗基因的影响

高胰岛素-正常血糖钳夹技术

定量分析

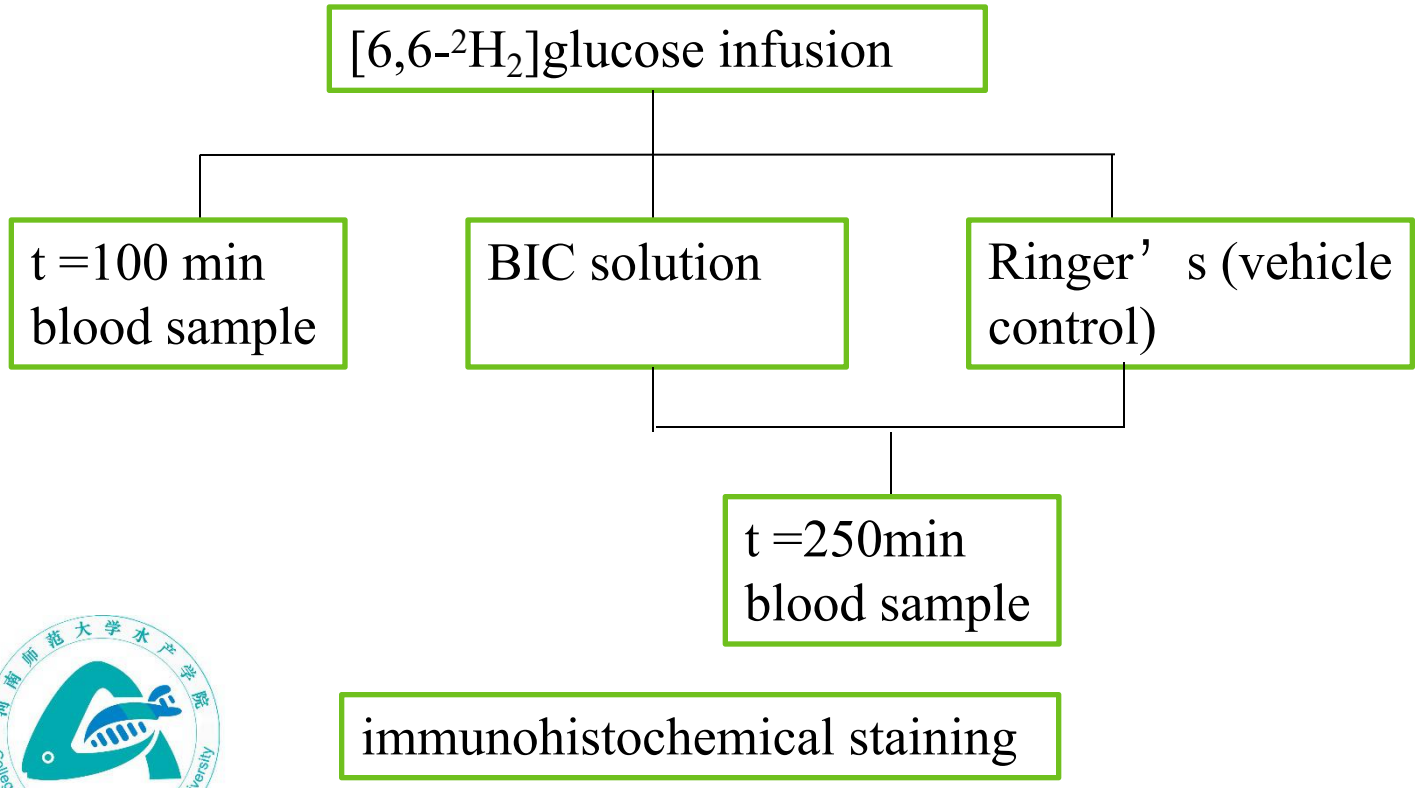
Pepck、G6Pase、GK、TNF、IL-6

下丘脑食欲素神经元对大鼠糖代谢的主要作用

研究方法

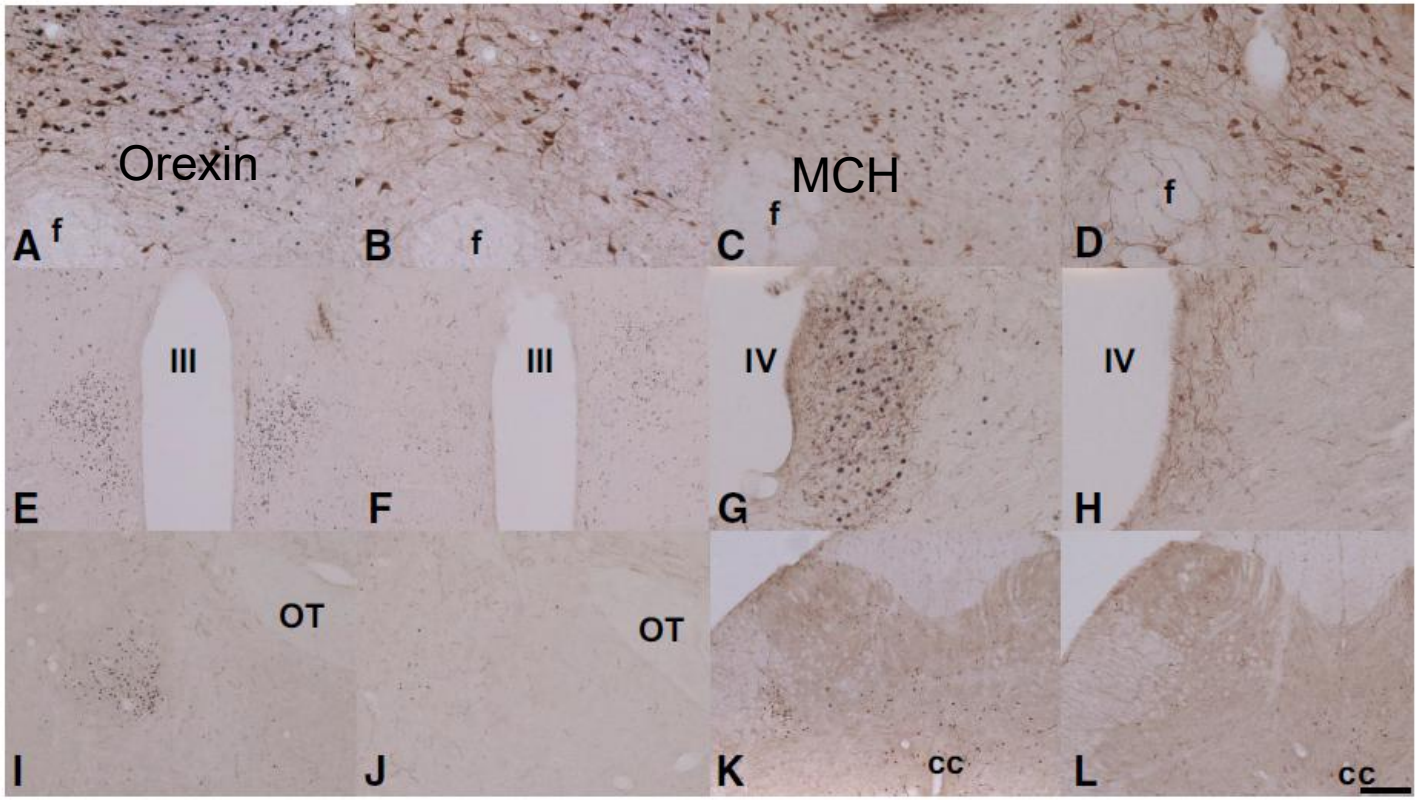
Experiment 1:

激活食欲素神经元是否对葡萄糖代谢产生影响。



结果

Result --去除下丘脑食欲素神经元内源性抑制剂GABA能够刺激内源葡萄糖产生(experiment1)



A,C,D:PF-Oa. B:dDMH.　E,G,I,K:食欲素靶向区域(orexin target areas）.

结果

Result --去除下丘脑食欲素神经元内源性抑制剂GABA能够刺激内源葡萄糖产生(experiment 1)

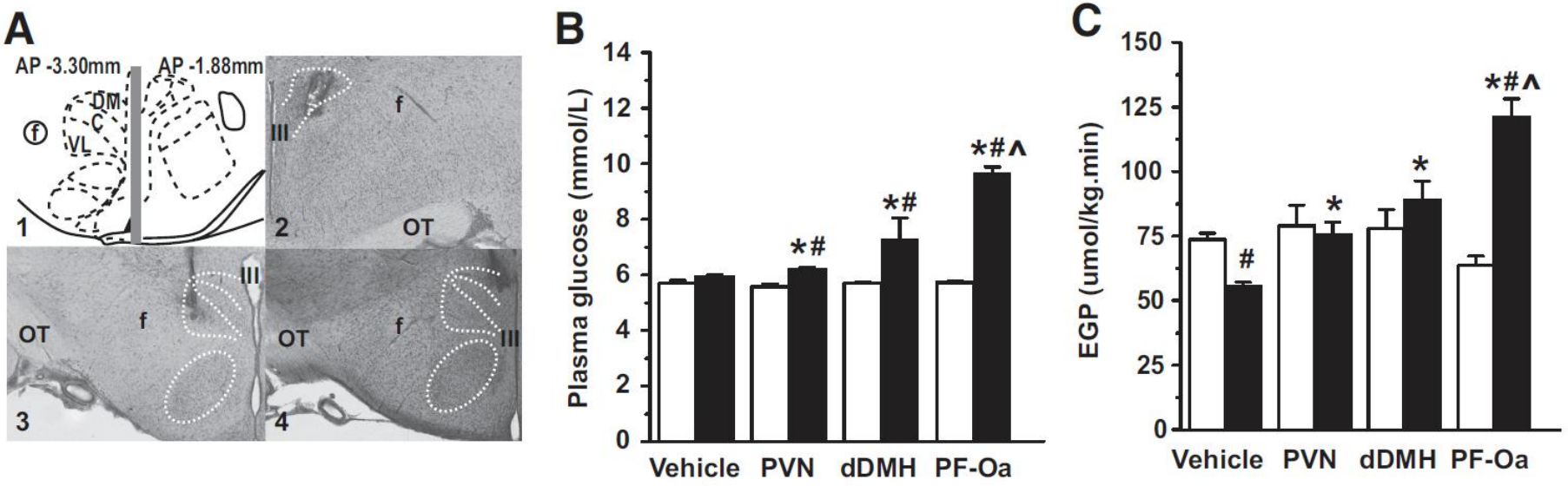


FIG. 1. GABAa receptor antagonist BIC administration in the PVN, dDMH, or PF Oa causes different EGP responses that are independent of changes in plasma insulin and corticosterone.Data are presented as means= SE. #P < 0.05 vs. equilibration state; *P < 0.05vs. vehicle control; ^P < 0.05 vs. dDMH and PVN.

结果

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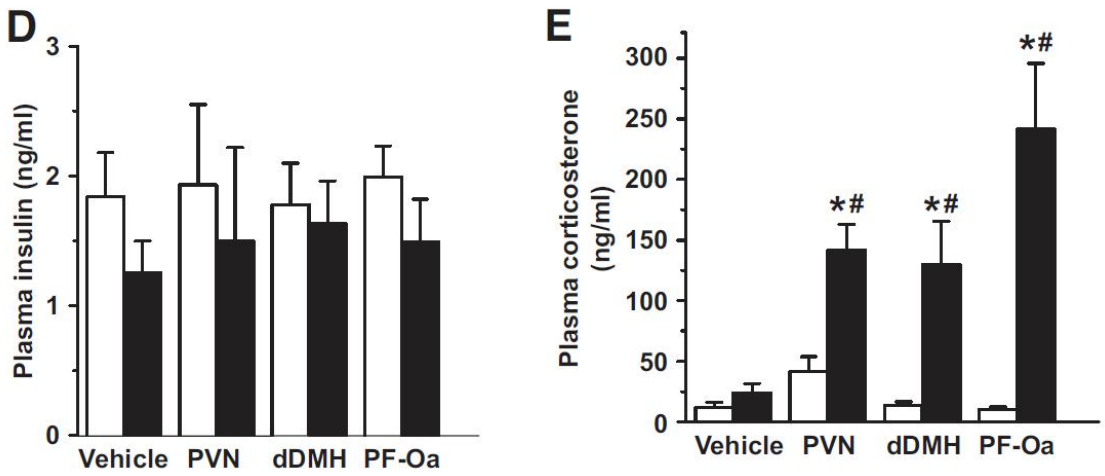

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结果

Experiment 1:

激活食欲素神经元是否对葡萄糖代谢产生影响。

结论:

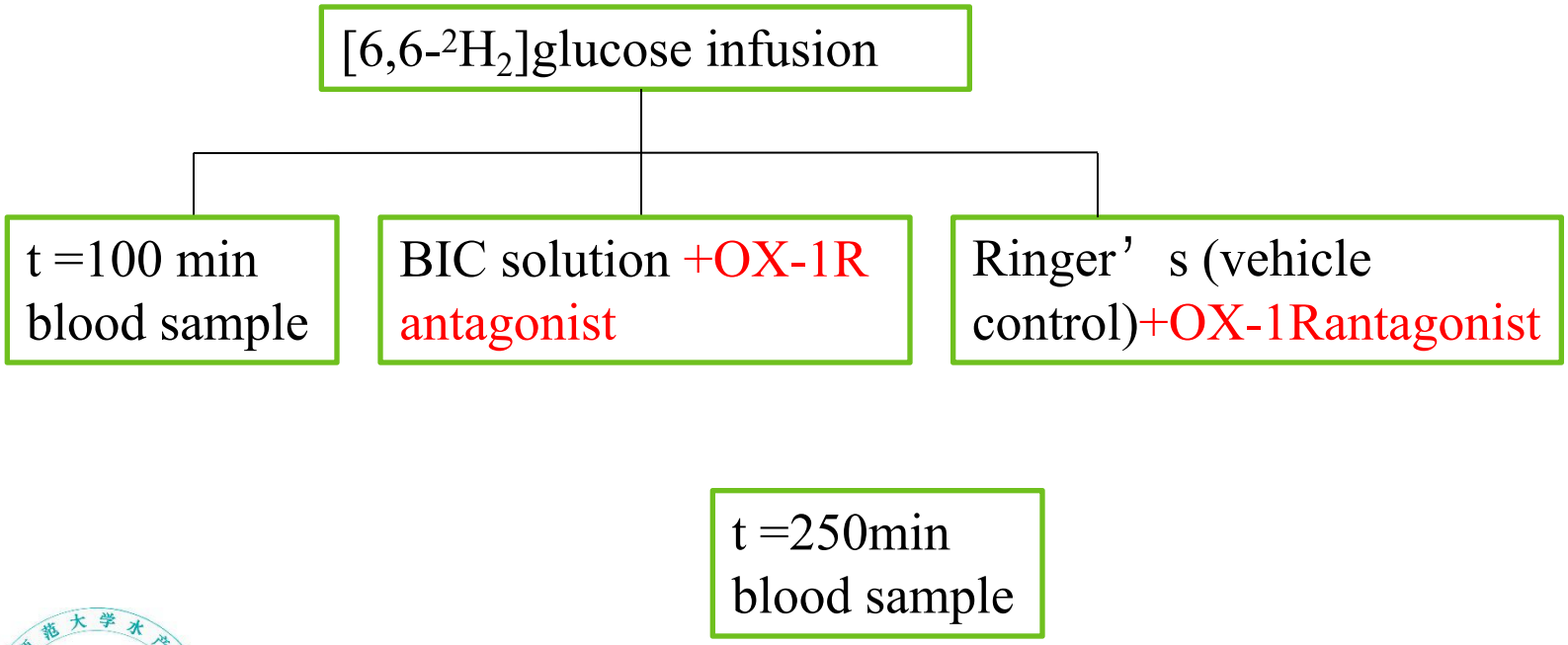
食欲素神经元在调控EGP方面起着重要的作用。

大部分PF Oa的食欲素神经元延伸到外侧DMH。

研究方法

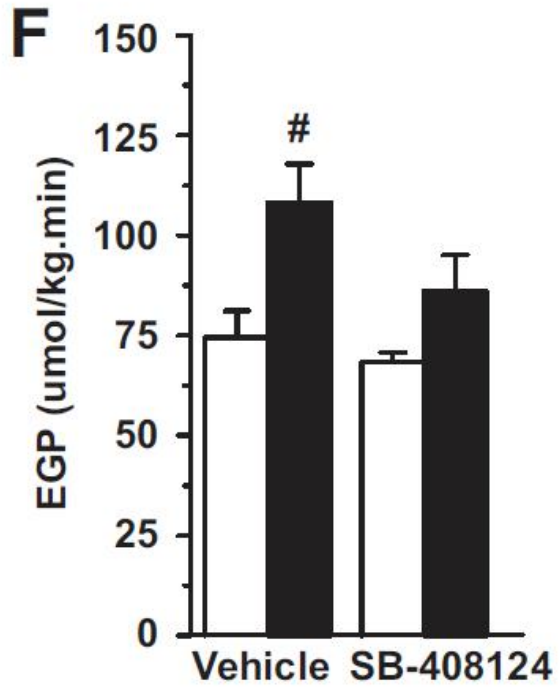
Experiment 2:

验证食欲素神经元的激活是否通过Orexin-A影响糖代谢。



结果

Result --Antagonizing the central orexin-1 receptor prevents the increase in EGP induced by BIC administration in the PF-Oa.



F: Average EGP beforeand after a 2-h infusion of BIC in the PF-Oa with intracerebroventricular vehicle or orexin-1 receptor antagonist SB-408124 (pre)treatment.Data are presented as means SE. #P < 0.05 vs. equilibration state; *P < 0.05vs. vehicle control; ^P < 0.05 vs. dDMH and PVN.

结果

Experiment 2:

验证食欲素神经元的激活是否通过Orexin-A影响糖代谢。

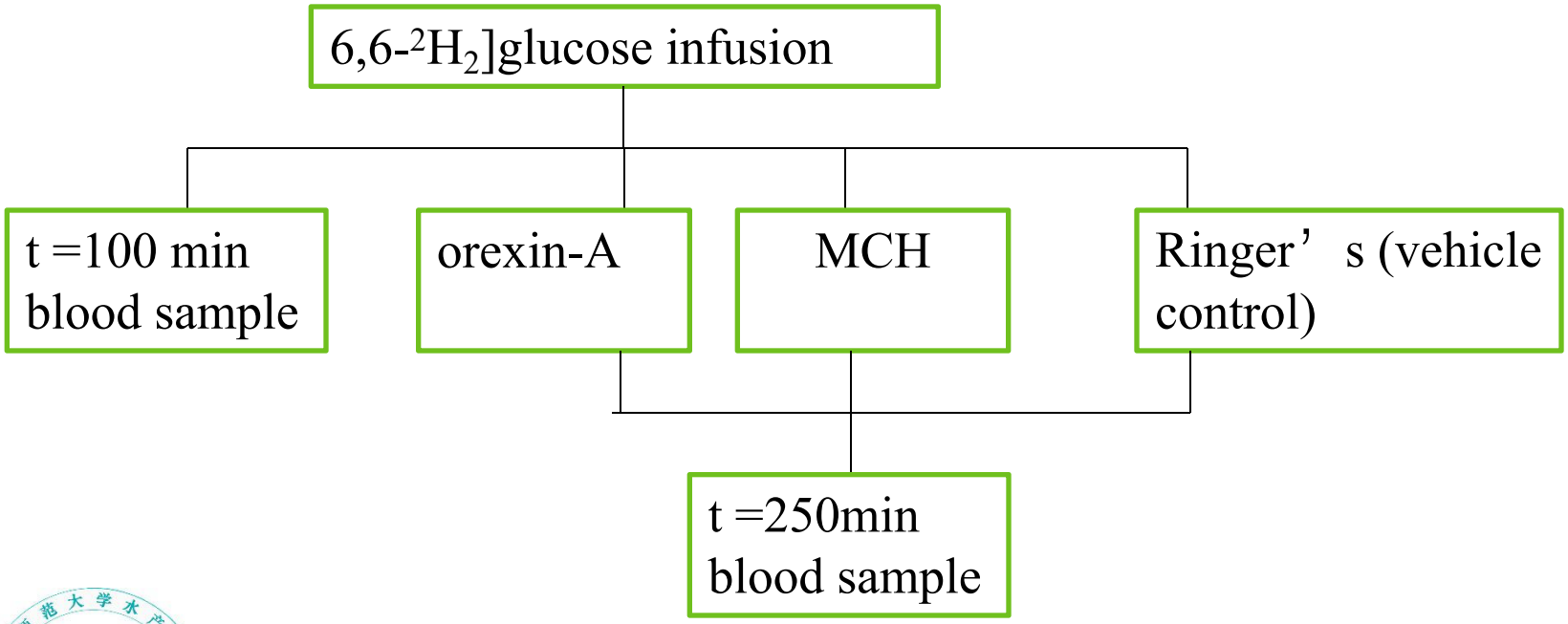
结论:

食欲素受体抑制剂阻止了BIC诱导的EGP增加，表明EGP的增加与食欲素有关。

研究方法

Experiment 3:

验证食欲素神经元的激活是否通过Orexin-A影响糖代谢。



结果

Result -- Central administration of orexin-A stimulates EGP(experiment 3).

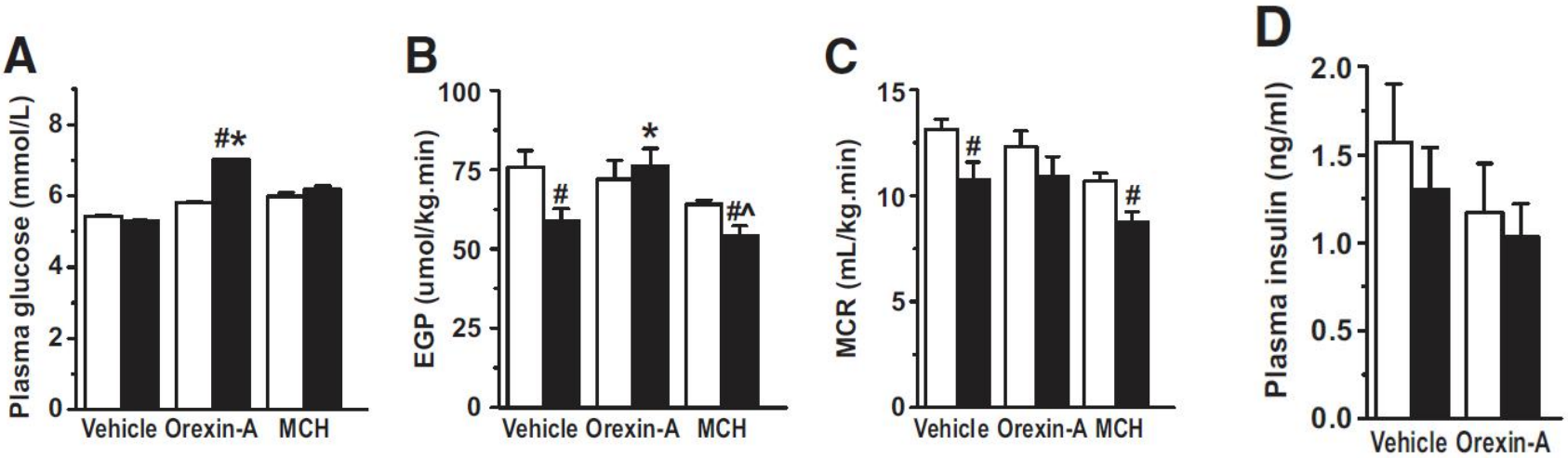


FIG. 3. A–C: Involvement of the autonomic nervous system in the EGP increase induced by BIC administration in the PF-Oa. Average plasma glucose concentration, EGP, and MCR before and after a 2-h infusion of vehicle, orexin-A, or MCH into the lateral cerebral ventricle. A–D:equilibrium state; f, intracerebroventricular infusion state. D: Average plasma insulin concentration before (equilibration state) and after intracerebroventricular vehicle or orexin-A infusion. *P < 0.05 vs. vehicle control in A and B and vs. HSX in G; ^P < 0.05 MCH vs.orexin-A group.

结果

Experiment 3：

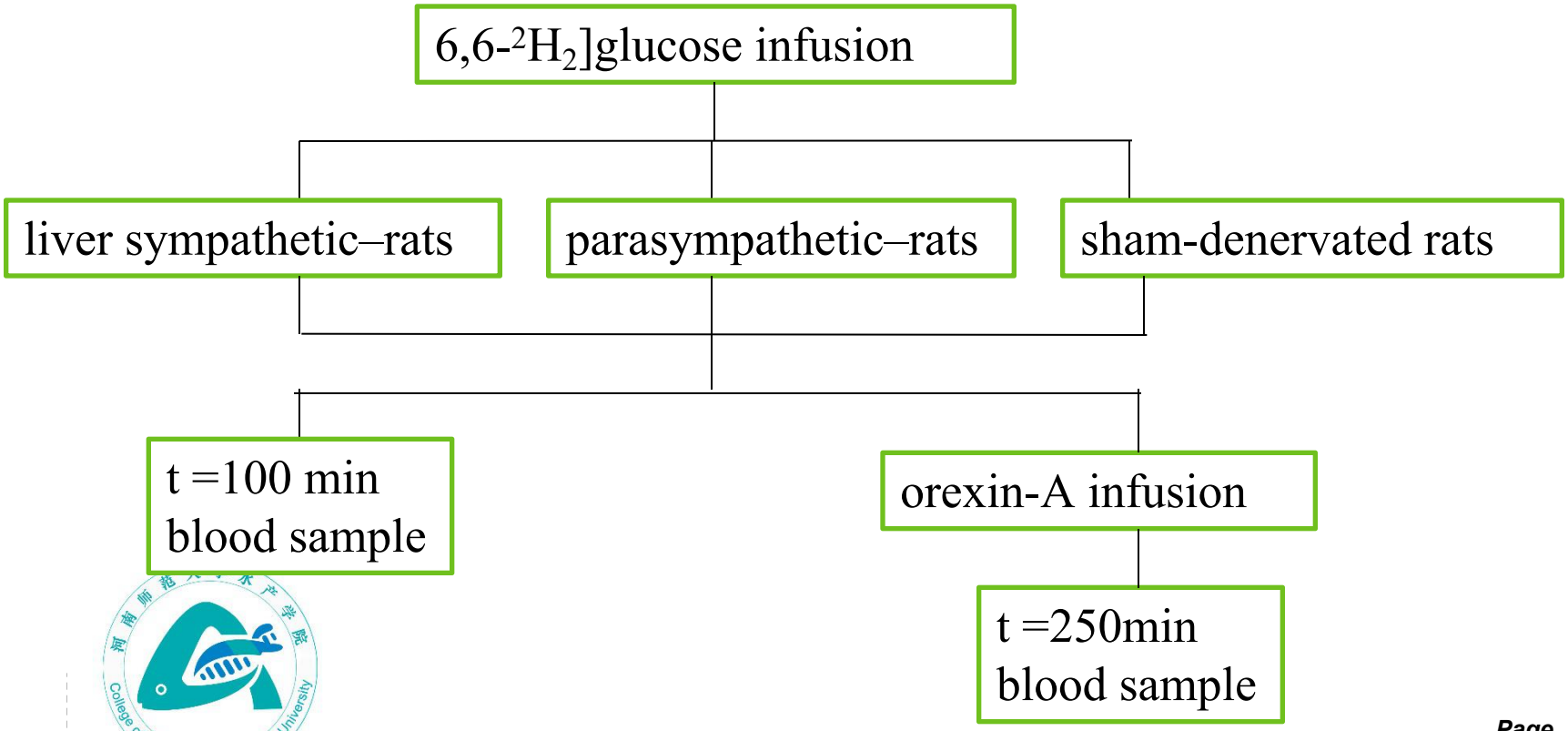
验证食欲素神经元的激活是否通过Orexin-A影响糖代谢。

结论：

脑室内输注食欲肽A增加了血浆葡萄糖水平及EGP。证明食欲素神经元确实参与了BIC诱导的EGP增加

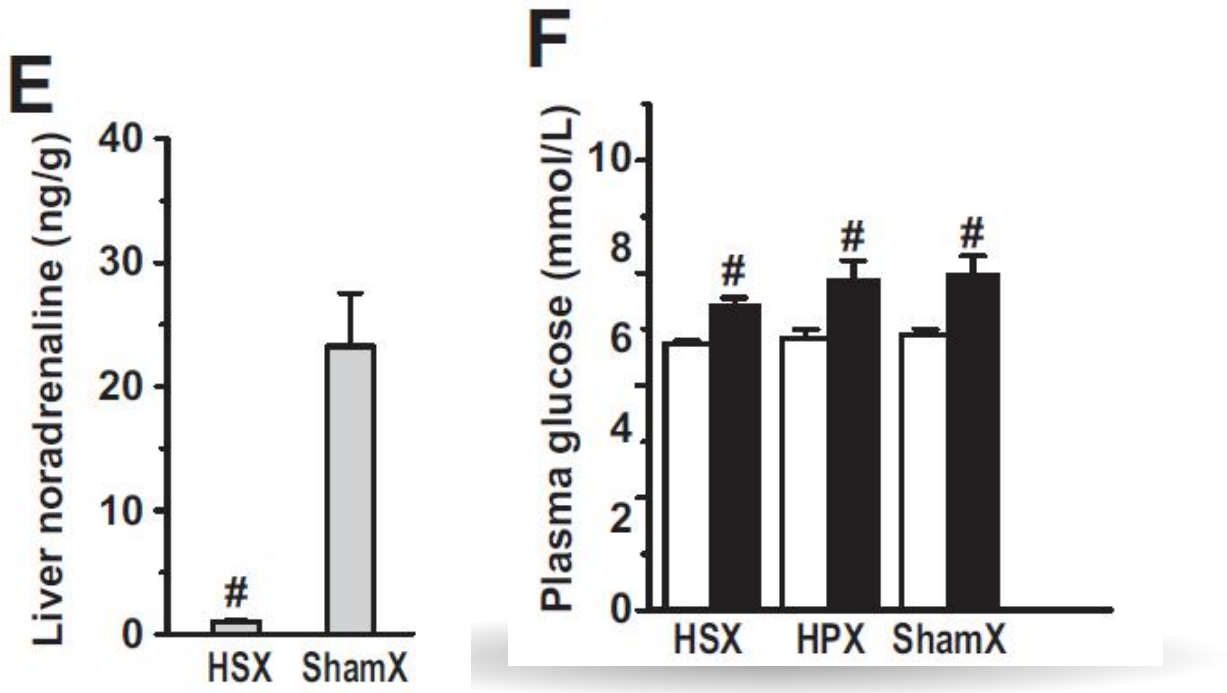
研究方法

Experiment 4:
肝脏去神经支配对内源葡萄糖产生的影响。



结果

Result -- Hepatic sympathetic, but not parasympathetic, denervation blocks the effect of intracerebroventricular orexin-A infusion on EGP (experiment 4).



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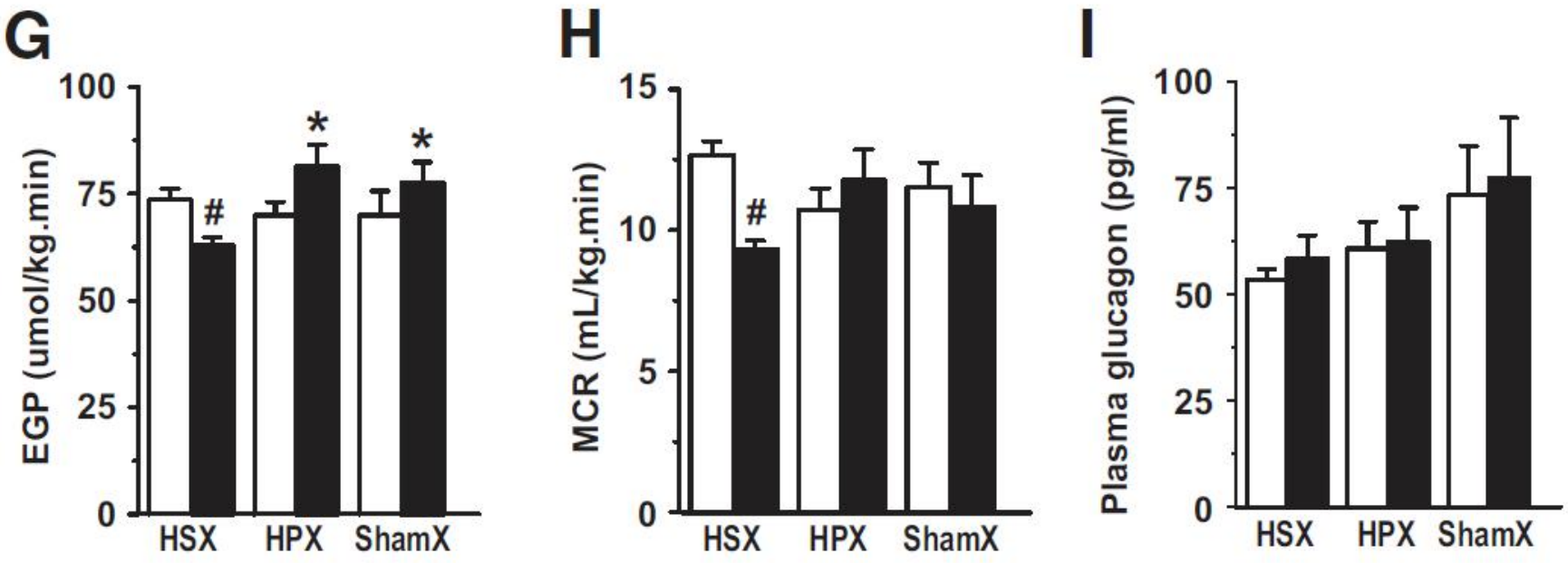


结果

Experiment 4:

肝脏去神经支配对内源葡萄糖产生的影响。

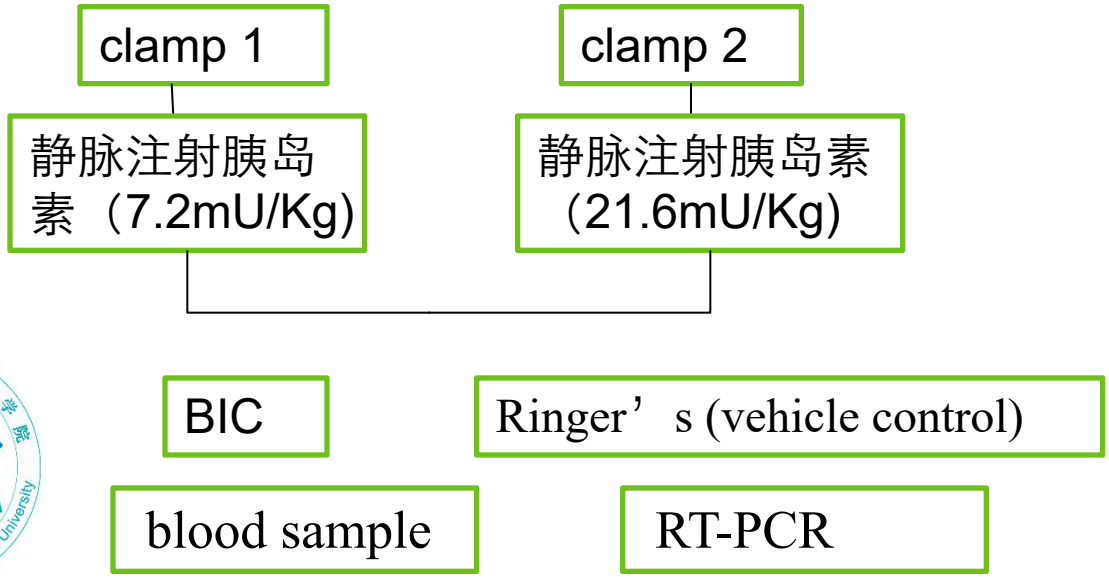
结论:

去除交感神经后，脑室内输注食欲肽A不再能够阻止EGP和MCR的下降，说明食欲素神经元刺激内源葡萄糖产生要通过交感神经。

研究方法

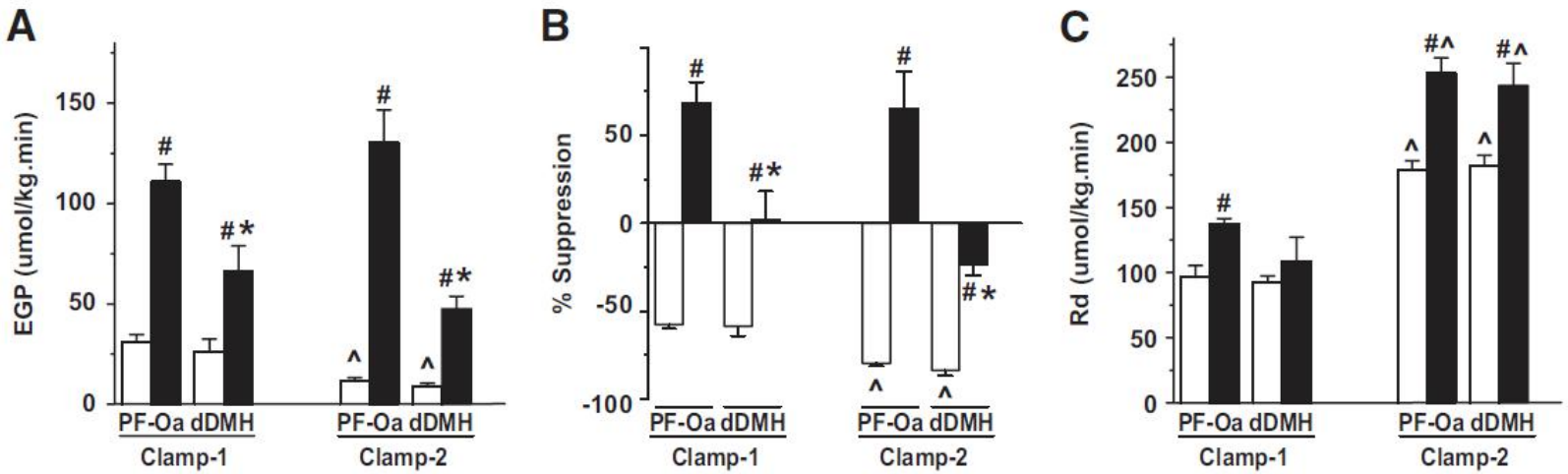
Experiment 5:
神经元食欲素对胰岛素及胰岛素抵抗基因的影响。

hyperinsulinemic-euglycemic clamp：高胰岛素-正常血糖钳夹技术,是一种定量检测胰岛素分泌和胰岛素抵抗的方法，是一种葡萄糖稳态的测量技术。



结果

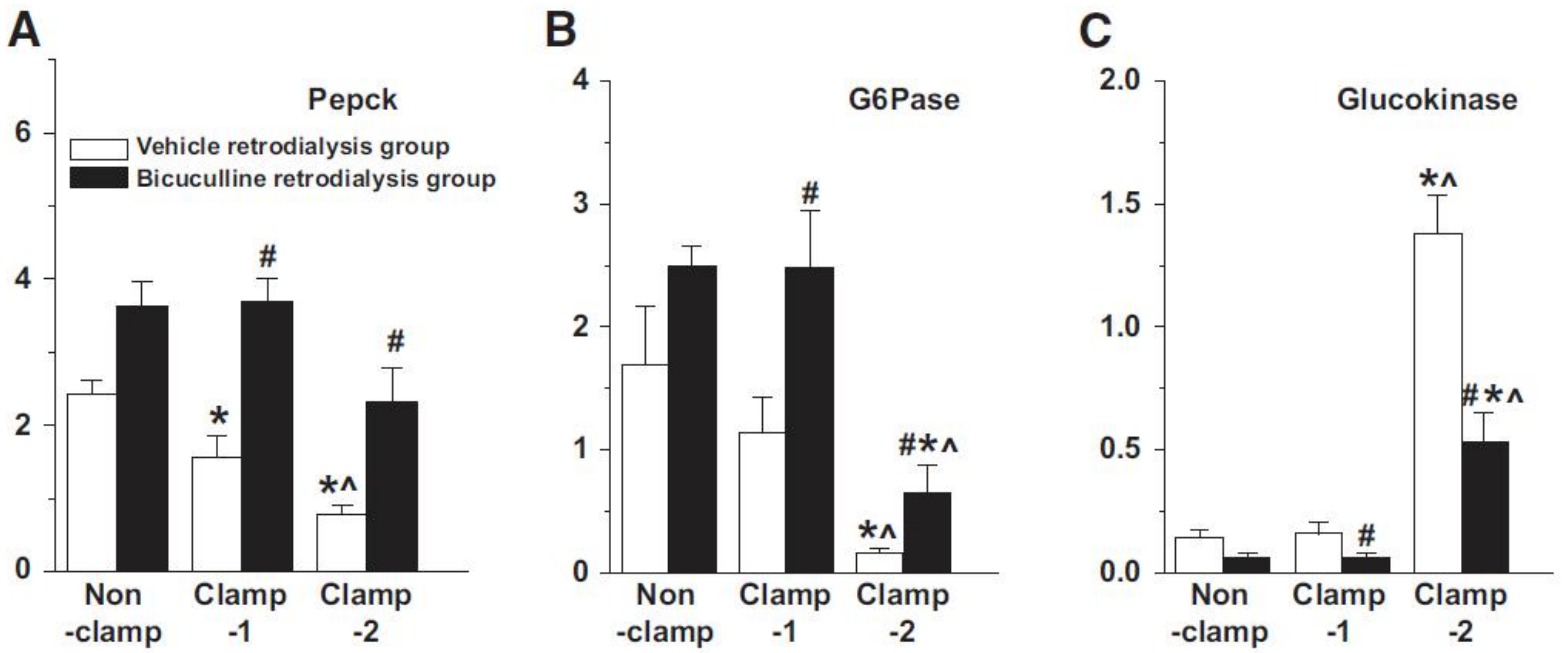
Result -- Removal of the endogenous GABA inhibition of perifornical orexin neurons reduces hepatic insulin sensitivity(experiment 5).



The rate of glucose disappearance (Rd)

结果

Result -- Removal of the endogenous GABA inhibition of perifornical orexin neurons reduces hepatic insulin sensitivity(experiment 5).



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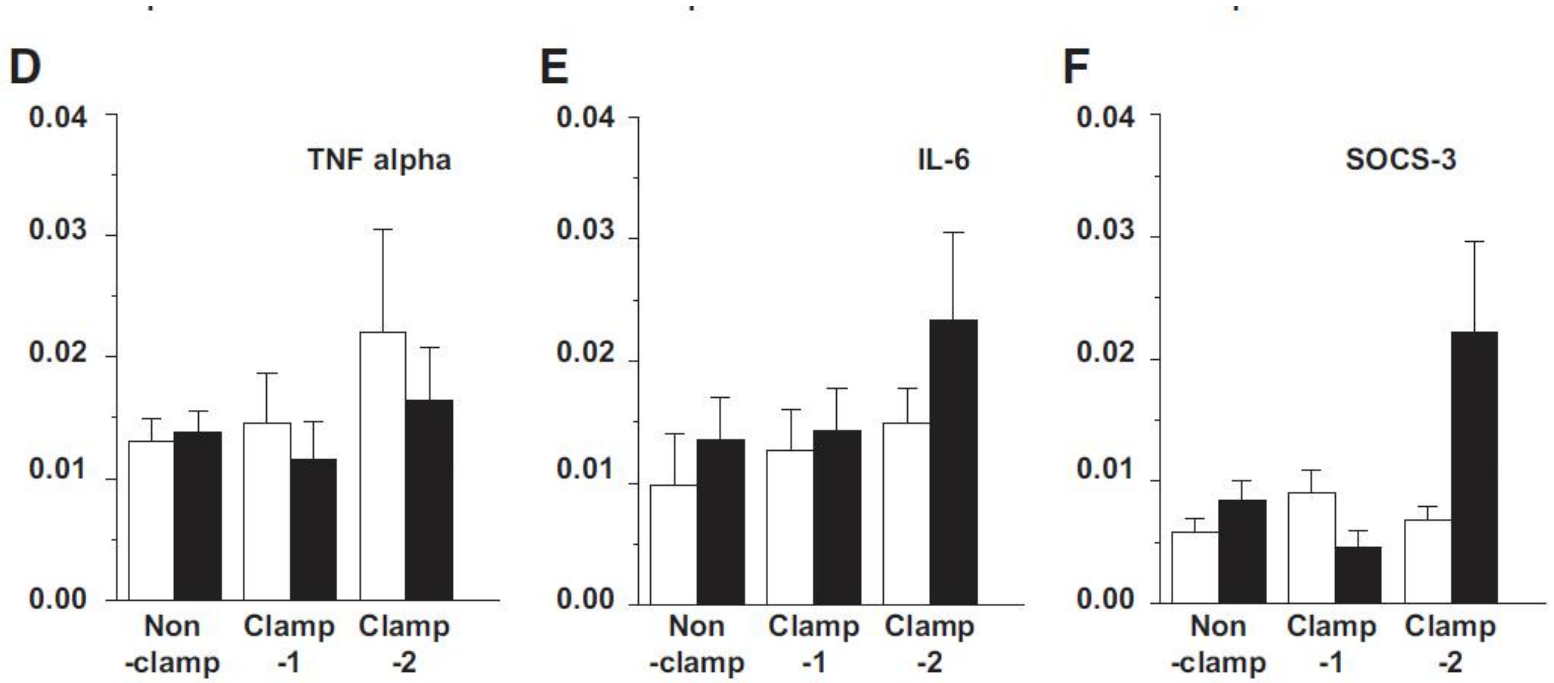


tumor necrosis factor(TNF), interleukin-6 (IL-6), suppressor of cytokine signaling (SOCS)-3

结果

Experiment 5：

神经元食欲素对胰岛素及胰岛素抵抗基因的影响。

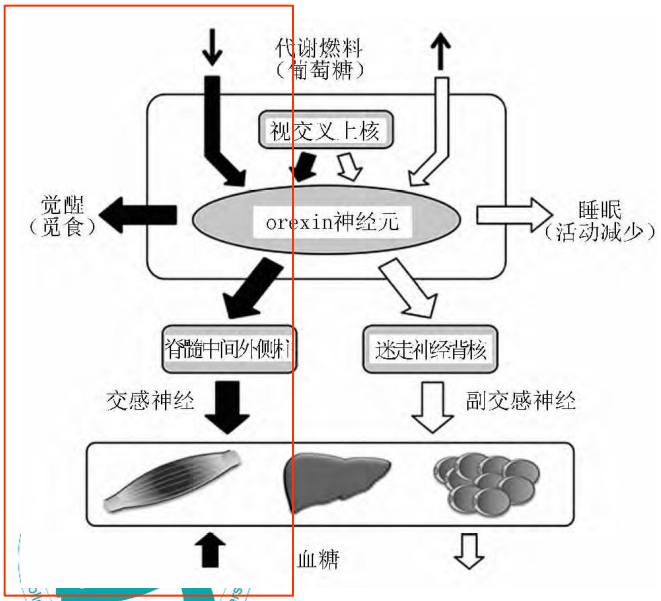
结论：

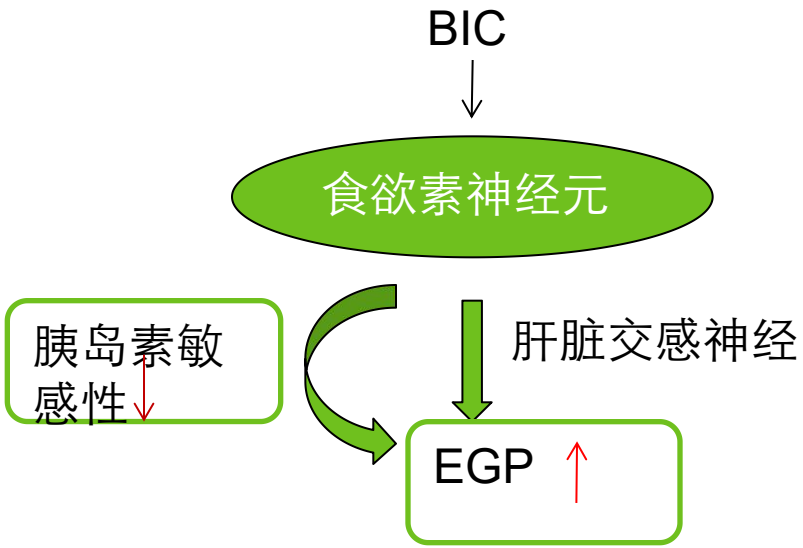
食欲素显著降低了高胰岛素对丙酮酸激酶（PEPCK）和葡萄糖-6-磷酸酶（G6Pase）表达的抑制作用并降低了其对葡萄糖激酶的促进作用。

BIC激活食欲素神经元使胰岛素敏感性降低。

总结

下丘脑食欲素是机体内葡萄糖平衡的重要调节因子。 目前的结果表明，食欲素神经元的激活将导致EGP的增加和肝胰岛素敏感性的降低，这种作用可能是通过交感神经系统产生。





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