读书报告

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胃肠肝病学

OPEN ACCESS

ORIGINAL ARTICLE

Apelin targets gut contraction to control glucose metabolism via the brain

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For numbered affiliations see end of article.

ABSTRACT

Objective The gut–brain axis is considered as a major regulatory checkpoint in the control of glucose homeostasis. The detection of nutrients and/or hormones in the duodenum informs the hypothalamus of the host's nutritional state. This process may occur via hypothalamic neurons modulating central release of

Significance of this study

What is already known on this subject?

▶ Circulating apelin is a bioactive peptide that exerts pleiotropic actions in various organs

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PART ONE

研究意义

Significance of this study

01 What is already known on this subject?

Apelin

The gut-to-brain axis is of crucial importance in the control of glucose homeostasis and is profoundly altered during metabolic diseases such as type 2 diabetes.

Enteric nervous system (ENS) is under the influence of various bioactive factors such as leptin, which is able to be transcytosed from the lumen to the gut wall.

Significance of this study

02

What are the new findings?

- **Luminal apelin is able to be transcytosed through the intestine to reach intraduodenal structures.**
- **Apelin controls ENS neurotransmitter release, that is, acetylcholine and nitric oxide, associated to variations of duodenal contraction.**
- **Apelin triggers ENS-induced duodenal contraction, leading to muscle glucose absorption via hypothalamic relay.**
- **Chronic oral administration of apelin improves glucose tolerance in closed correlation to a decrease in duodenal motility in normal and obese/diabetic mice.**

Significance of this study

03

How might it impact on clinical practice in the foreseeable future?

- **Modulation of the ENS/contraction of the duodenum is a new physiological system controlling peripheral glucose utilisation via the brain.**
- **oral apelin administration could be considered as a promising therapeutic target to treat insulin resistance state.**

PART TWO

方法

材料和方法

急性注射（Apelin，Apelin受体（APJ）拮抗剂，NOS抑制剂，β-肾上腺素能受体激动剂、烟碱受体拮抗剂和辣椒素）

Apelin慢性给药（口服）

胃内和脑室手术，

遥测、等张收缩，免疫组织化学，转运，乙酰胆碱的释放，葡萄糖和Apelin吸收，葡萄糖的利用率，定量PCR，代谢参数，胰岛素和Apelin测定、口服葡萄糖耐量试验

细胞培养与荧光显微镜

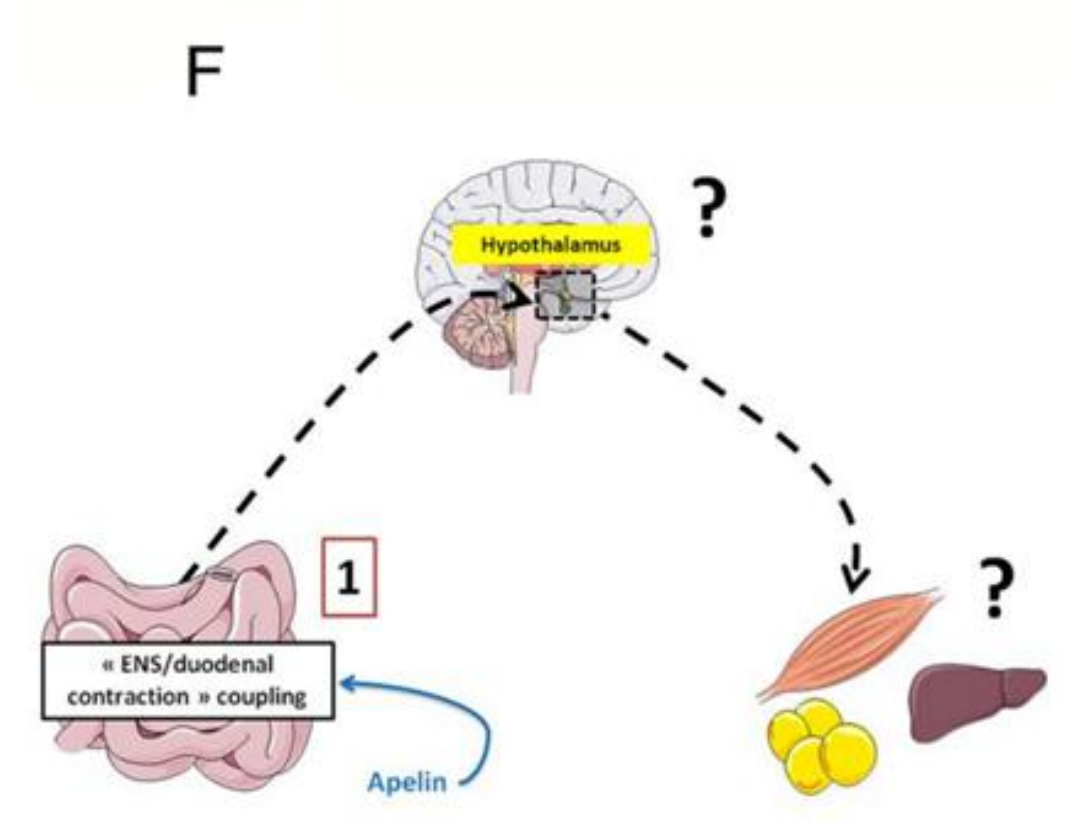
离体十二指肠实时NO测量

下丘脑实时NO测量

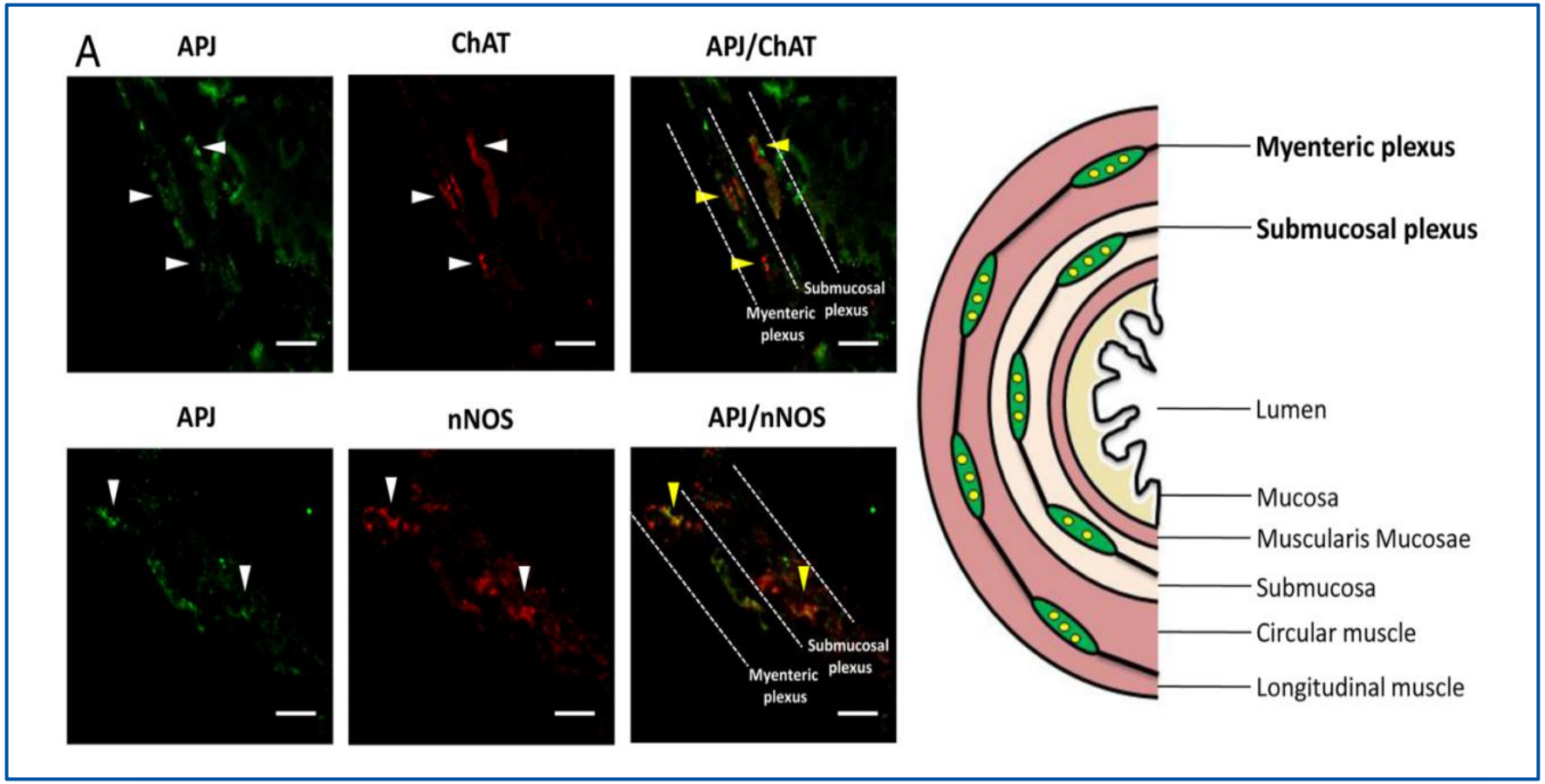
PART THREE

结果

1. Apelin acts on ENS neurons to control duodenal contractions



1. Apelin acts on ENS neurons to control duodenal contractions



肌间神经丛

粘膜下神经丛

肠腔

肠粘膜
粘膜肌层
粘膜下层

环形肌

纵肌

Figure 1 A : apelin 受体APJ 在ChAT 和nNOS 神经元上表达

1. Apelin acts on ENS neurons to control duodenal contractions

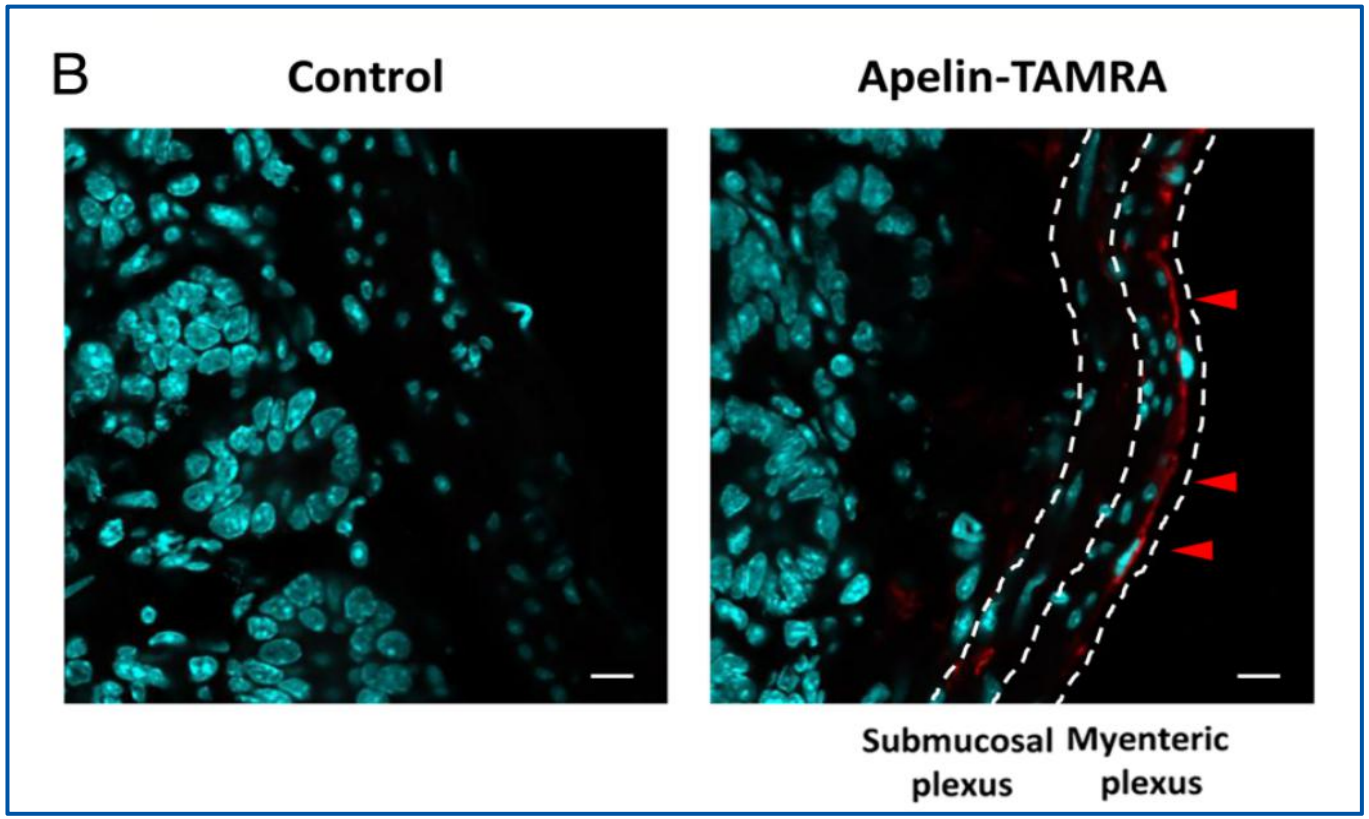


Figure 1 B : apelin能够跨细胞转运，从神经丛到达组织细胞

1. Apelin acts on ENS neurons to control duodenal contractions

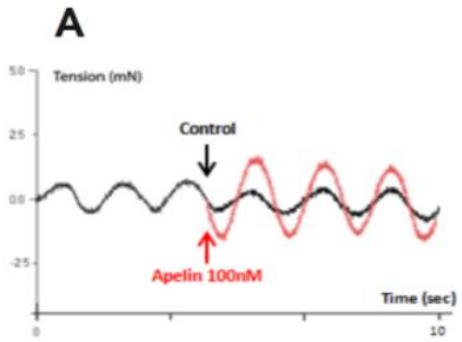
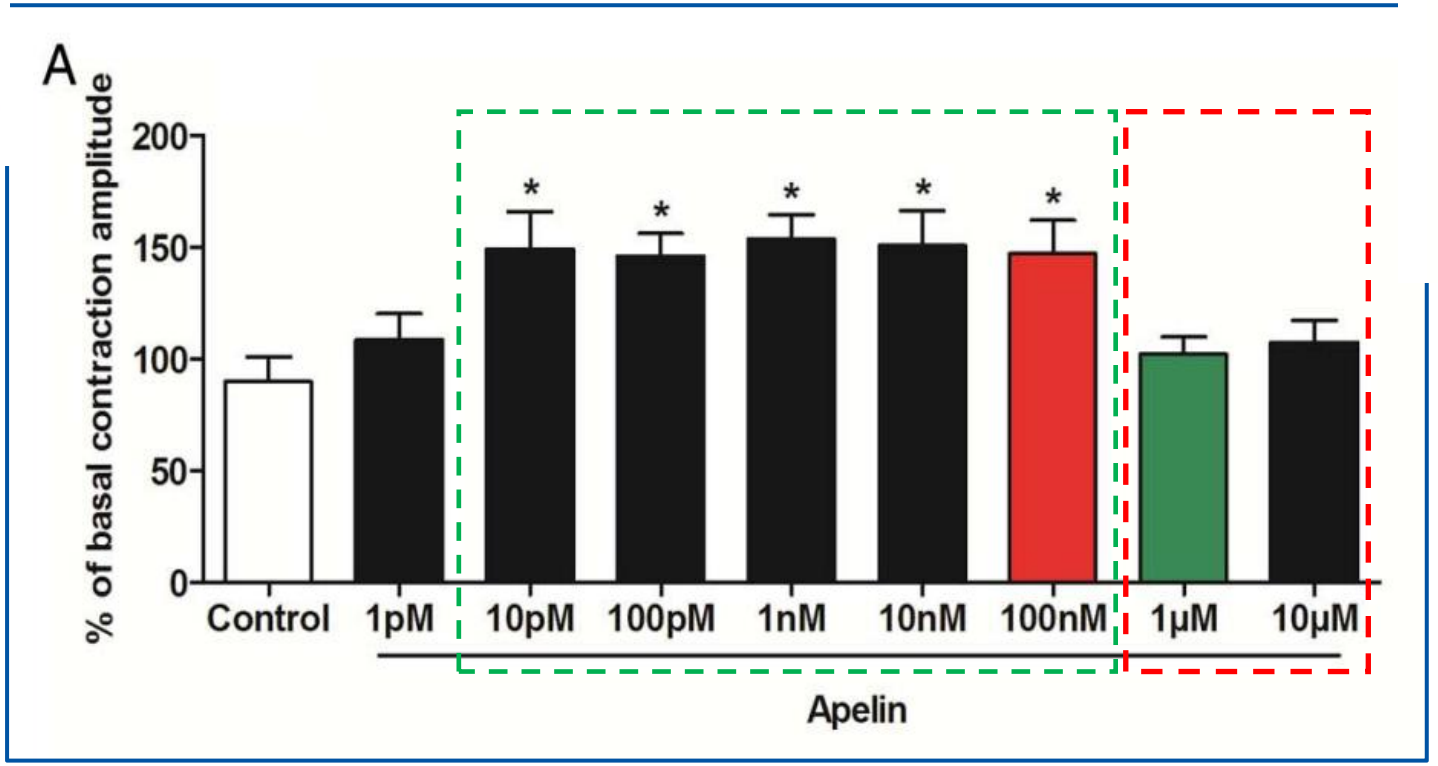


Figure S2 A：记录（代表）



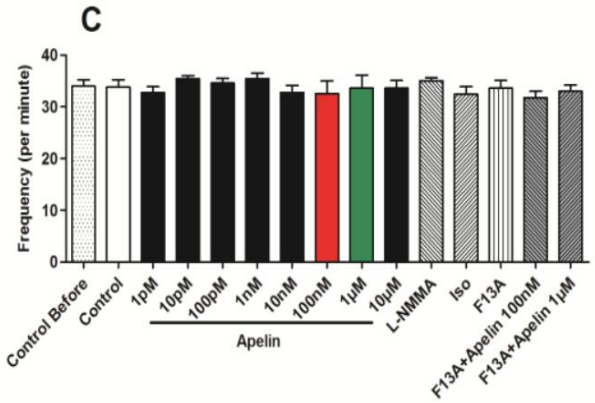


Figure S2 C：频率变化

Figure 2 A：体外十二指肠样本注射Apelin (1 pM to 10 μM)振幅变化

1. Apelin acts on ENS neurons to control duodenal contractions

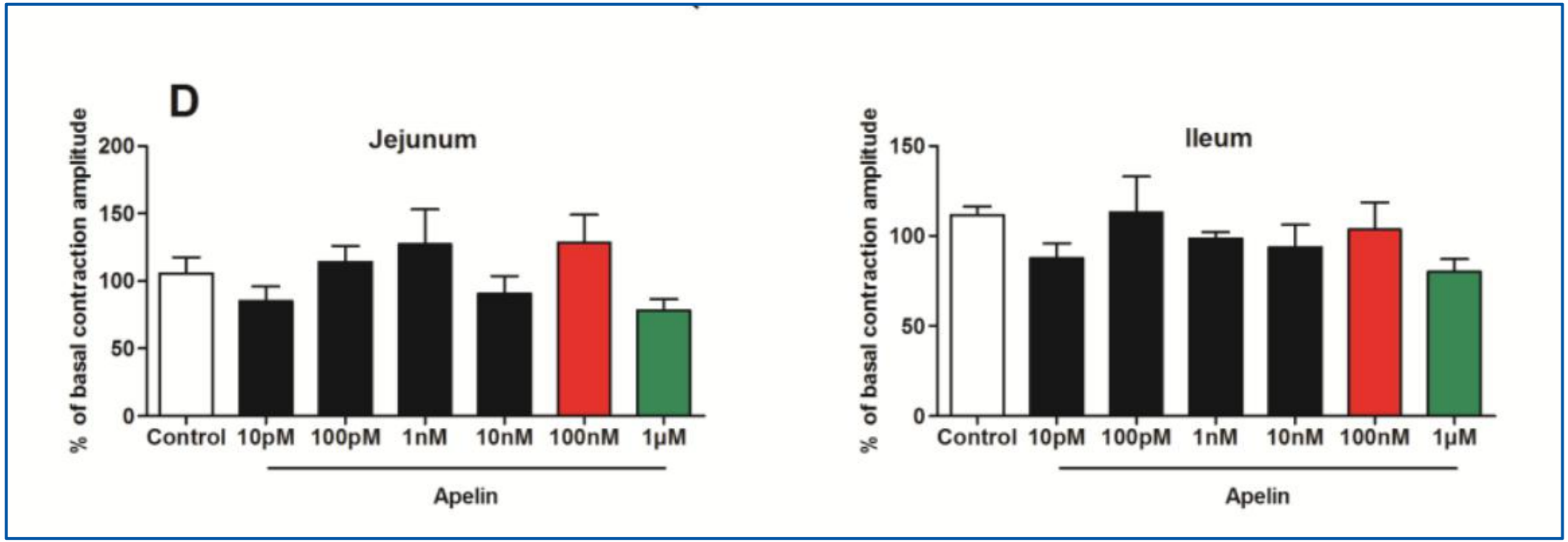


Figure S2 D:Apelin对十二指肠的调节具有特异性，因为其对空肠和回肠的收缩没有影响

1. Apelin acts on ENS neurons to control duodenal contractions

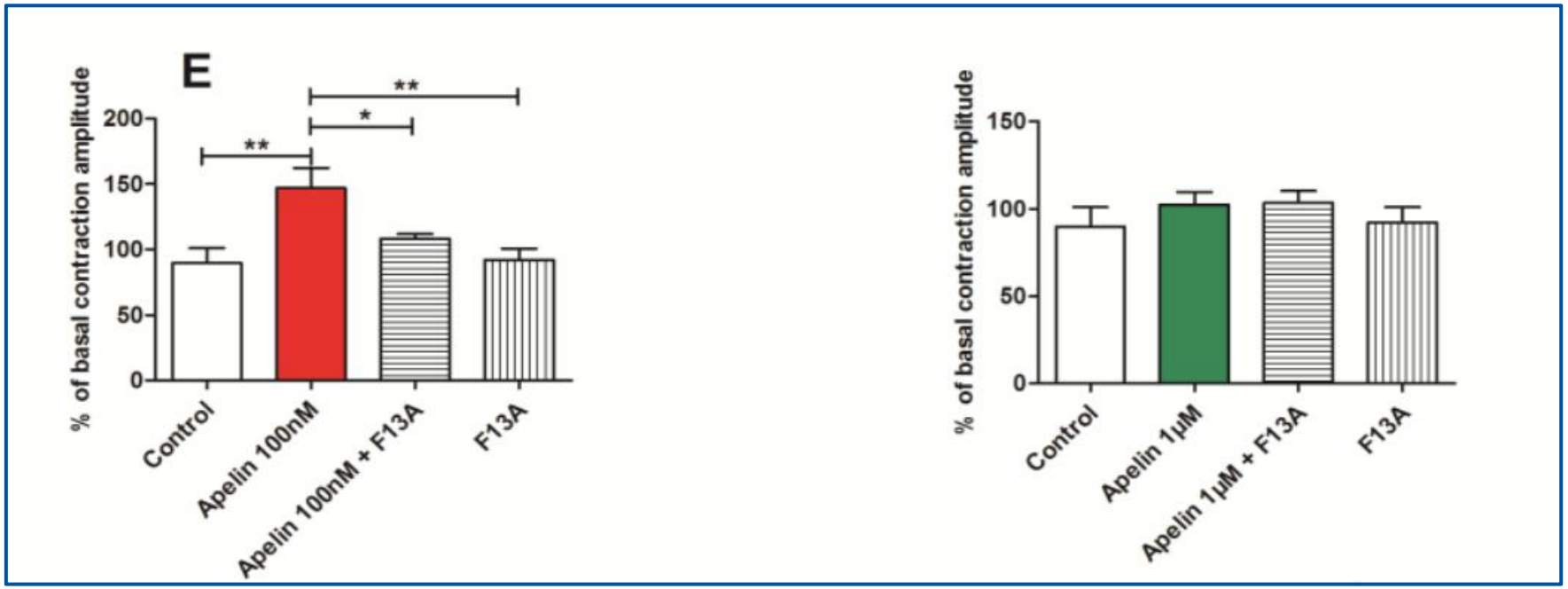


Figure S2 E:两种剂量存在两种不同的信号通路，都被F13A拮抗。

1. Apelin acts on ENS neurons to control duodenal contractions

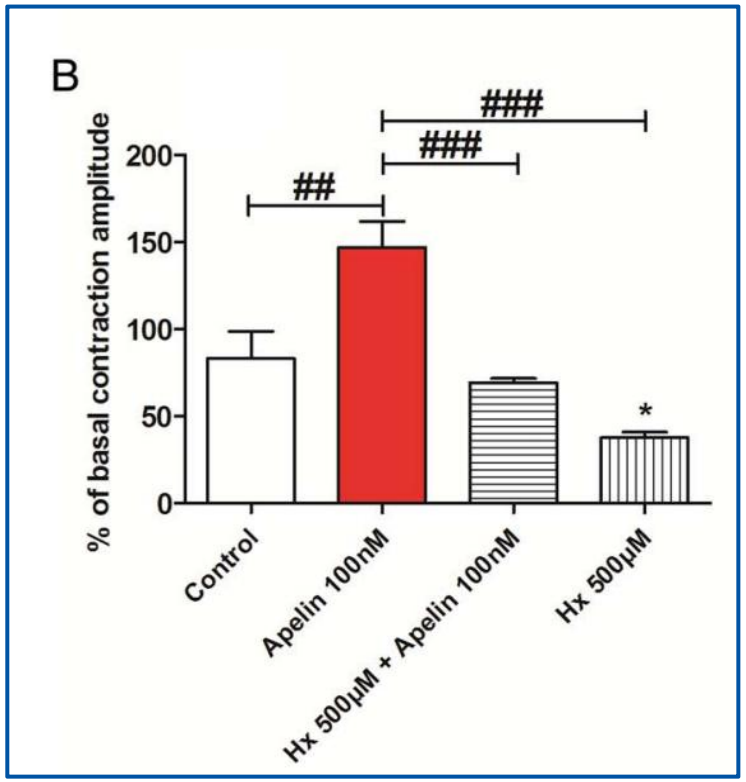
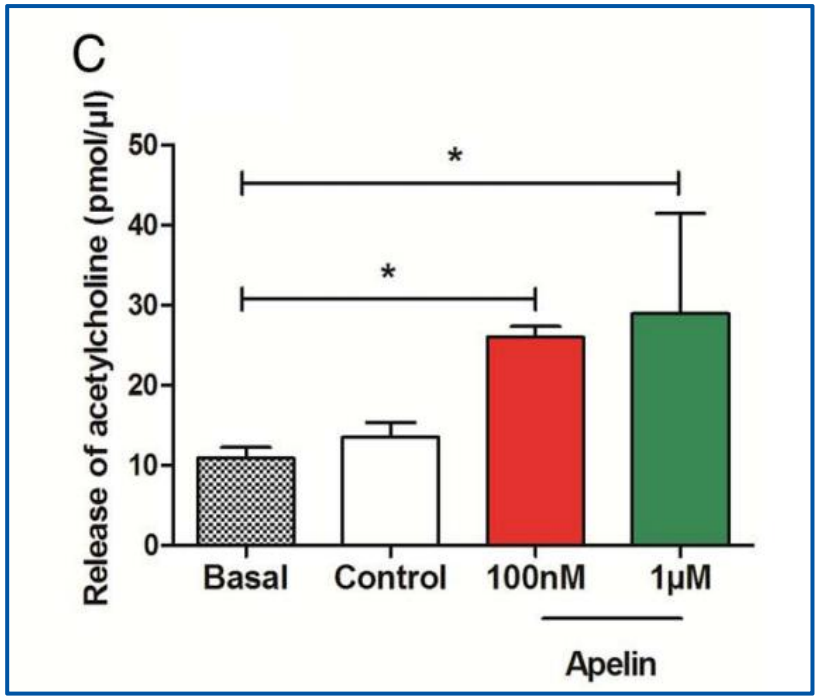
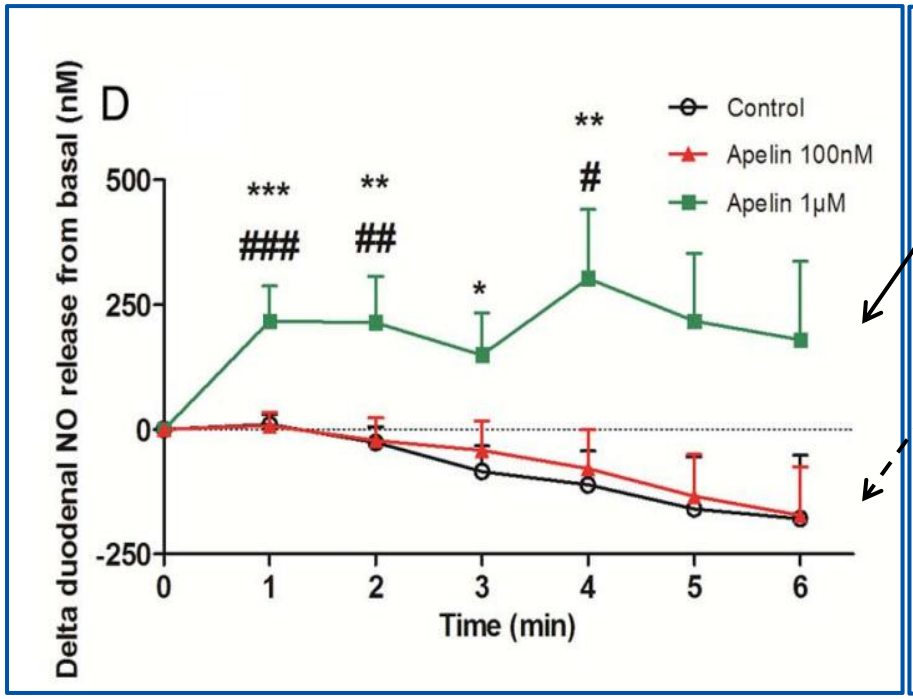


Figure 2 B: Apelin（100nM）对肠道收缩的刺激作用，需要ChAT神经元

1. Apelin acts on ENS neurons to control duodenal contractions





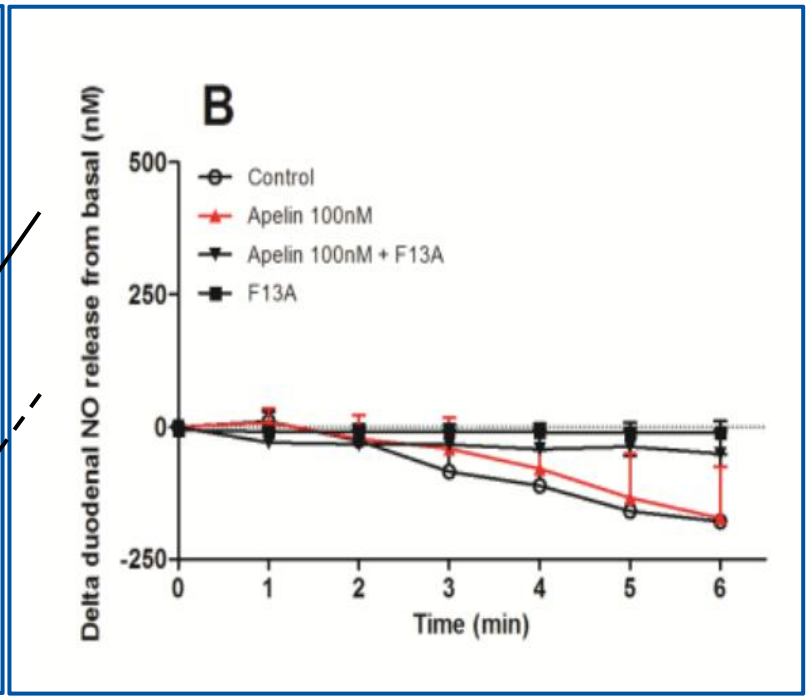
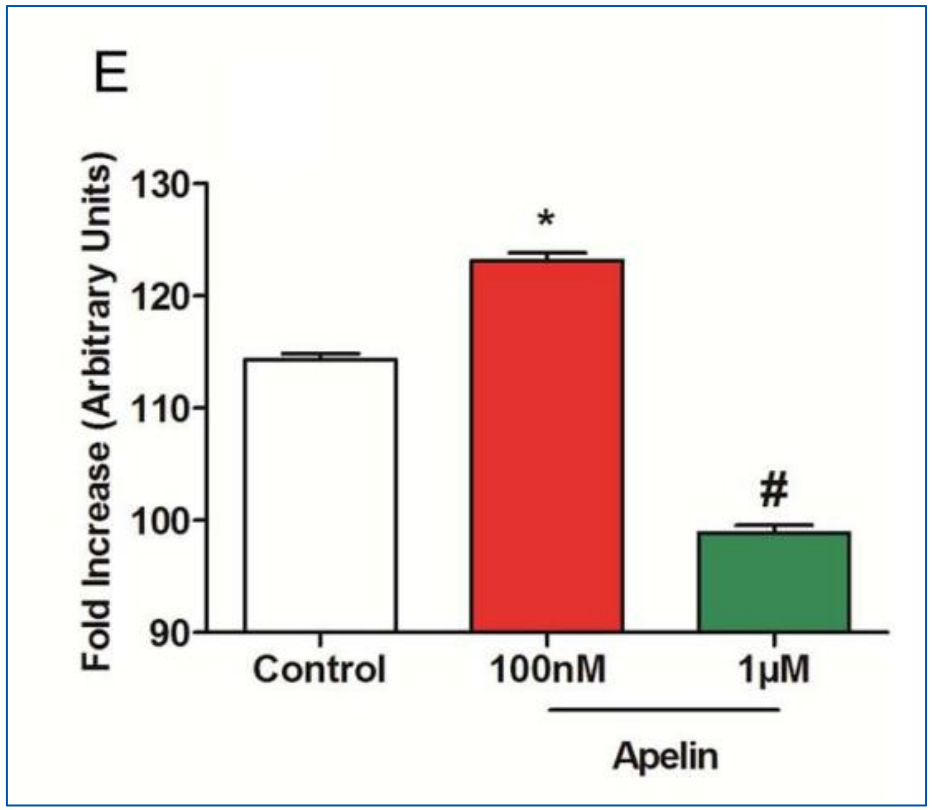


Figure 2 C：apelin（100 nM or 1 µM ）对十二指肠乙酰胆碱释放的影响

Figure 2 D：apelin（100 nM or 1 µM ）对十二指肠NO释放的影响

Figure S3B：apelin（100 nM or 1 µM ）对十二指肠NO的释放的影响受到拮抗剂阻断

1. Apelin acts on ENS neurons to control duodenal contractions



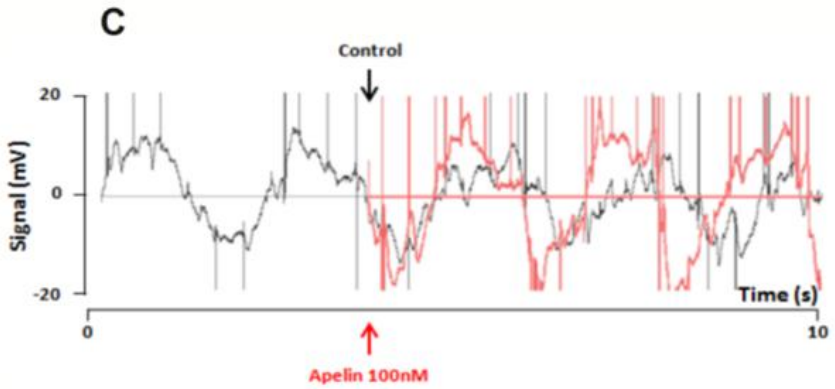


Fig S3C: 肠道活动实时监测

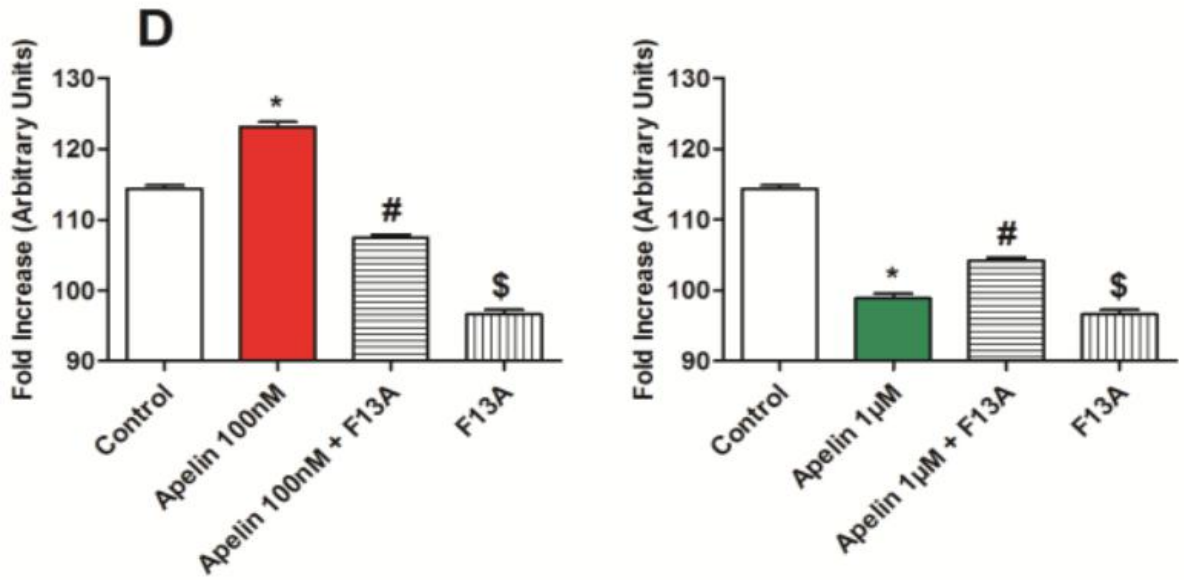


Figure 2 E: Apelin 100 nm引起十二指肠电活动显著增加，而1 μM减少了这种活动

1. Apelin acts on ENS neurons to control duodenal contractions

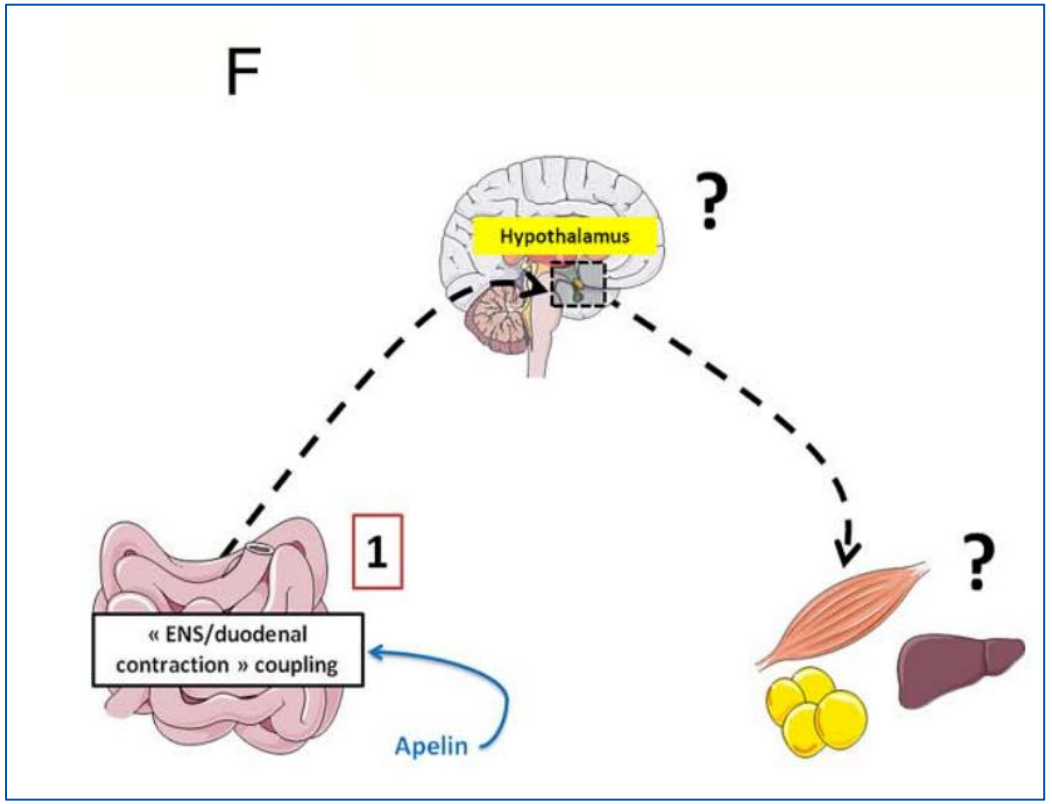


Figure 2F：Apelin通过调节ENS活动改变十二指肠收缩。

1. Apelin acts on ENS neurons to control duodenal contractions

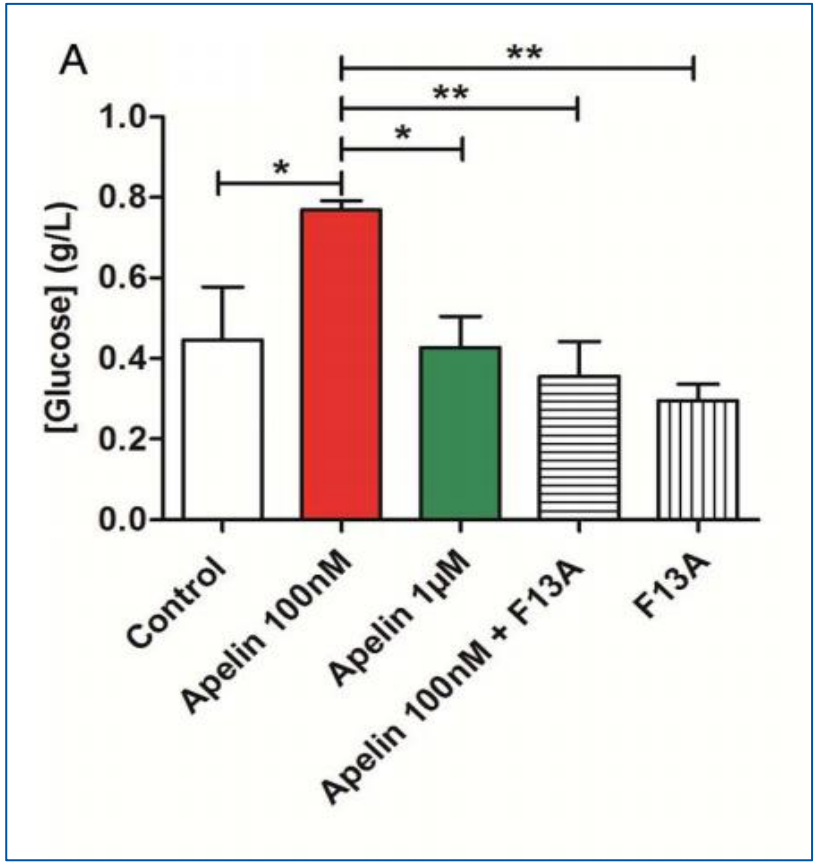


Figure 3A：apelin 100 nm增加了十二指肠葡萄糖吸收，Apelin 1μM则起降低作用

1. Apelin acts on ENS neurons to control duodenal contractions

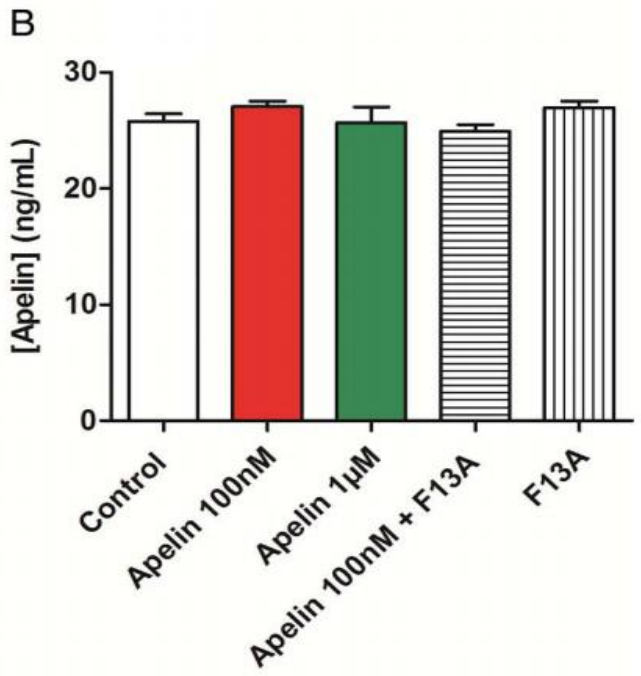


Fig 3B：处理对apelin吸收无影响

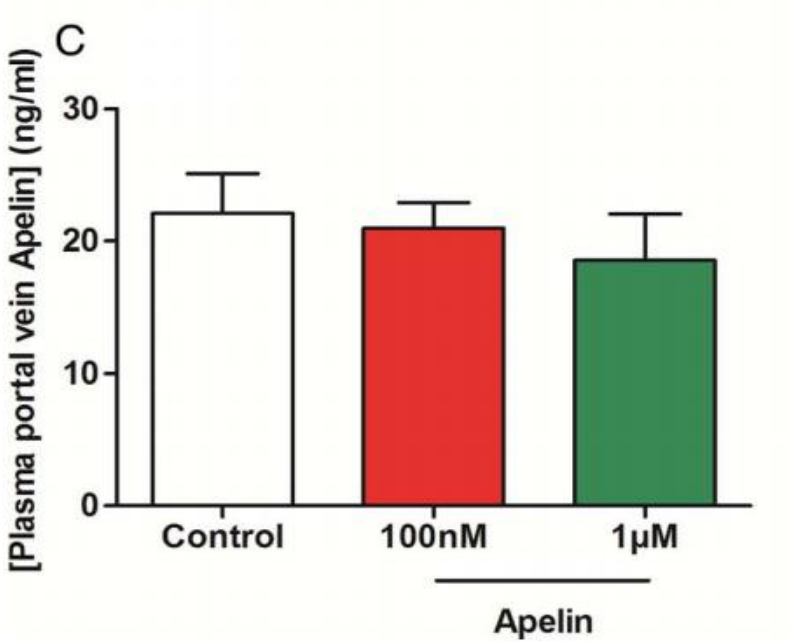


Fig 3C：apelin灌胃不改变门静脉中apelin浓度

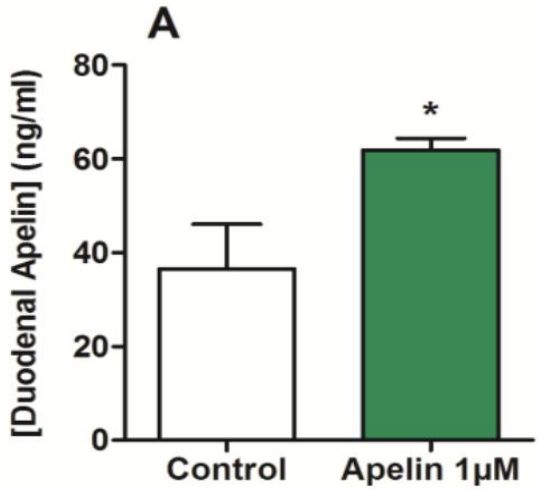
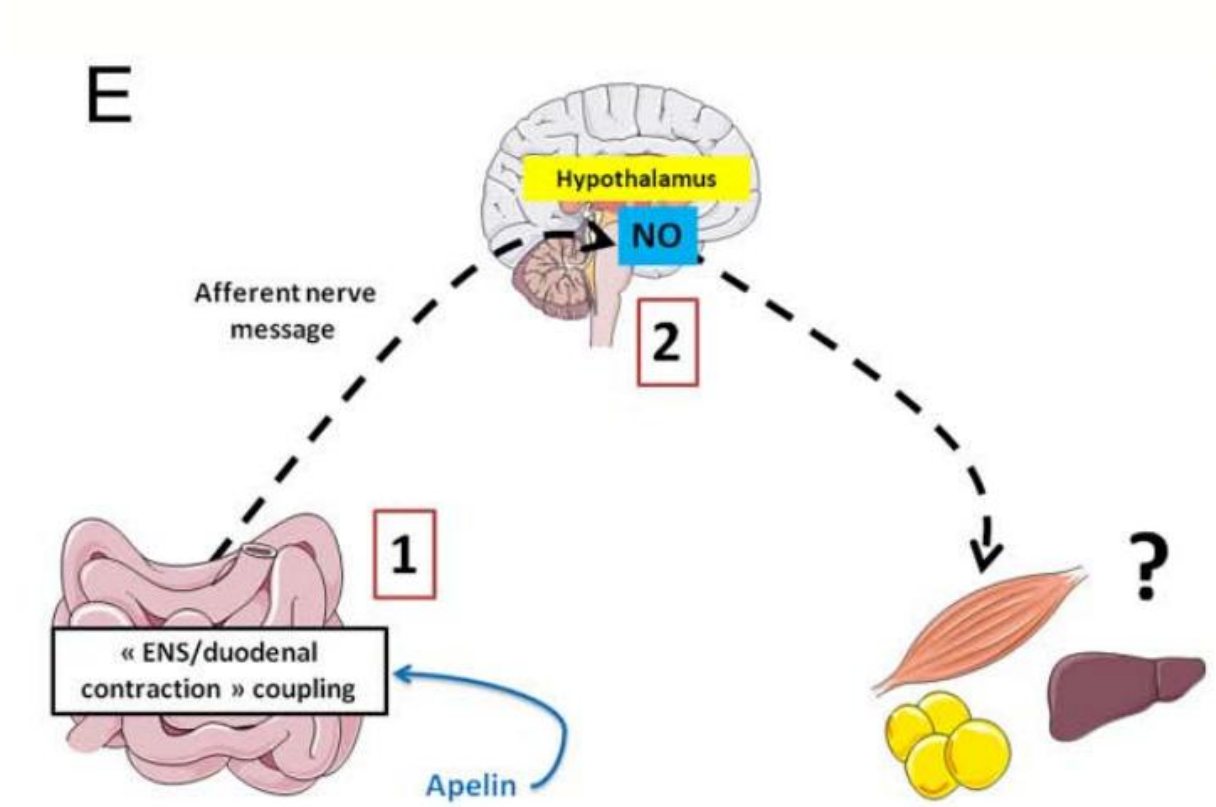


Fig S6A: 十二指肠壁apelin水平升高

Apelin特异性作用于十二指肠壁

2. Duodenal apelin controls hypothalamic NO release



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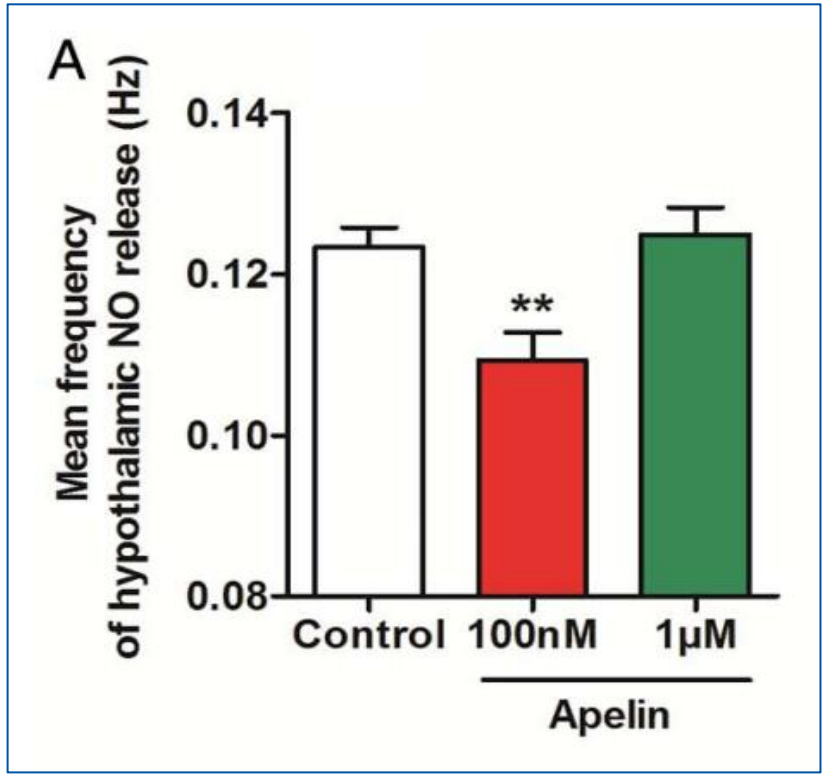


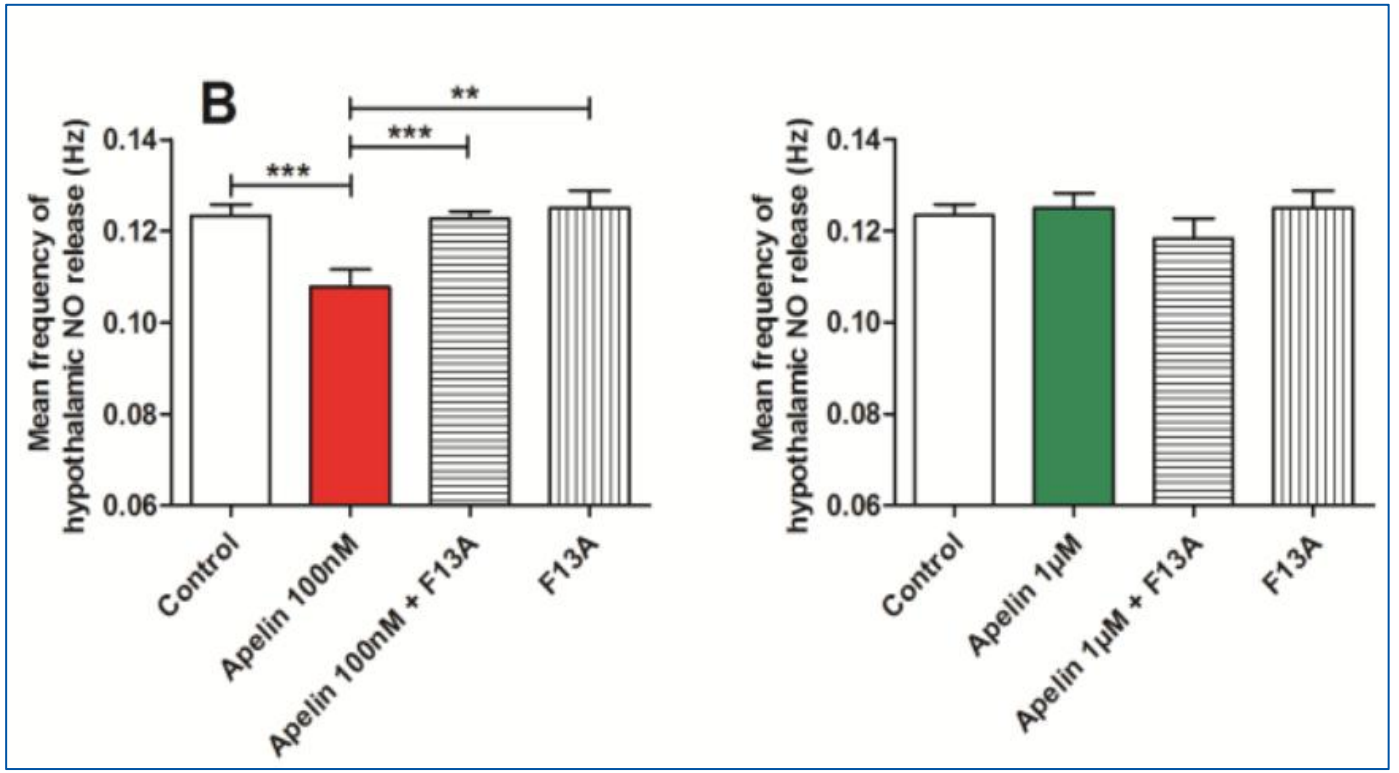


Fig 4A：apelin 100 nm/ 1μM对下丘脑NO释放频率的影响

Fig S4B：这种影响被APJ受体拮抗剂（F13A）阻断。

2. Duodenal apelin controls hypothalamic NO release

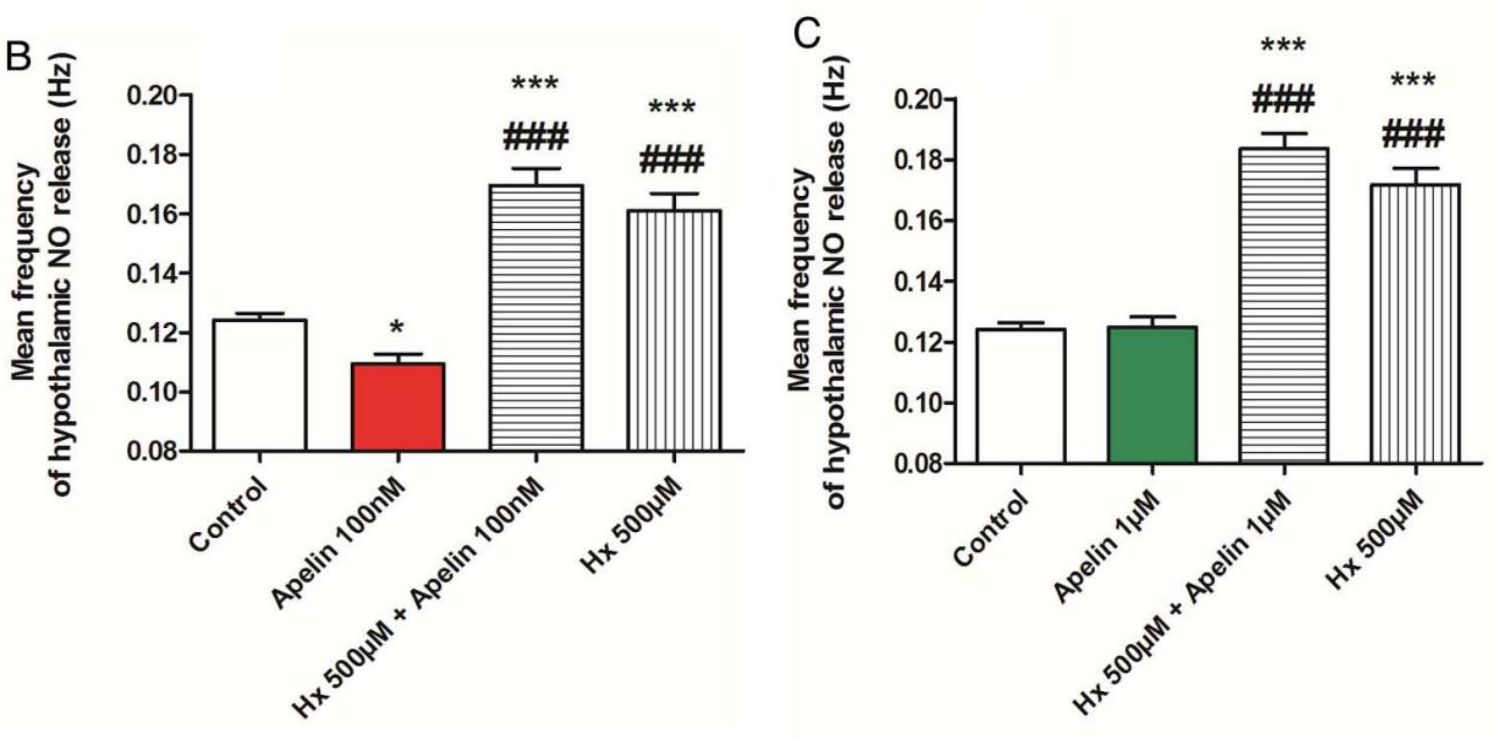


Fig 4B/C：用六甲胺阻断烟碱受体破坏 肠道apelin(100nM/ 1μM)对下丘脑NO释放频率的影响

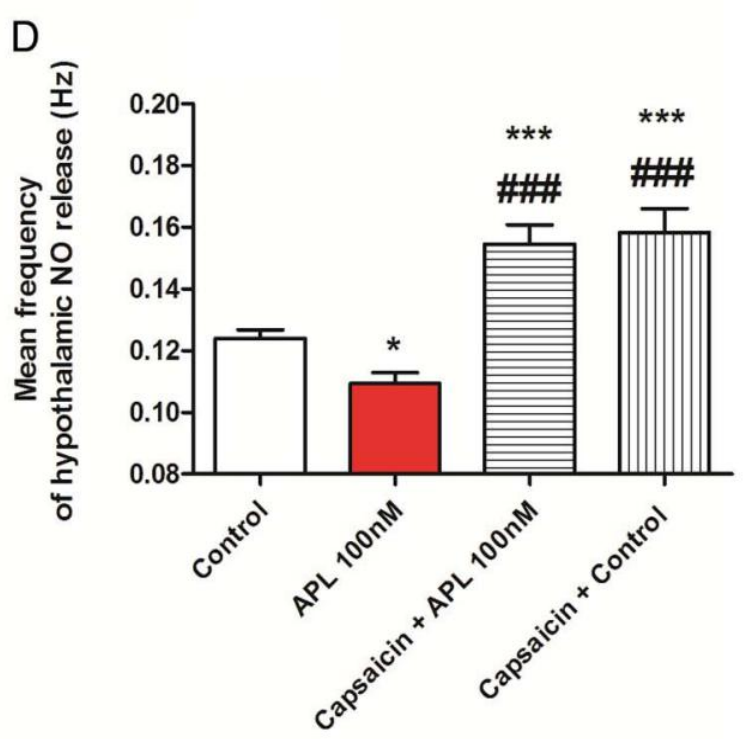


Fig 4D：用辣椒素破坏传入神经末梢破坏 肠道apelin(100nM)对下丘脑NO释放频率的影响

2. Duodenal apelin controls hypothalamic NO release

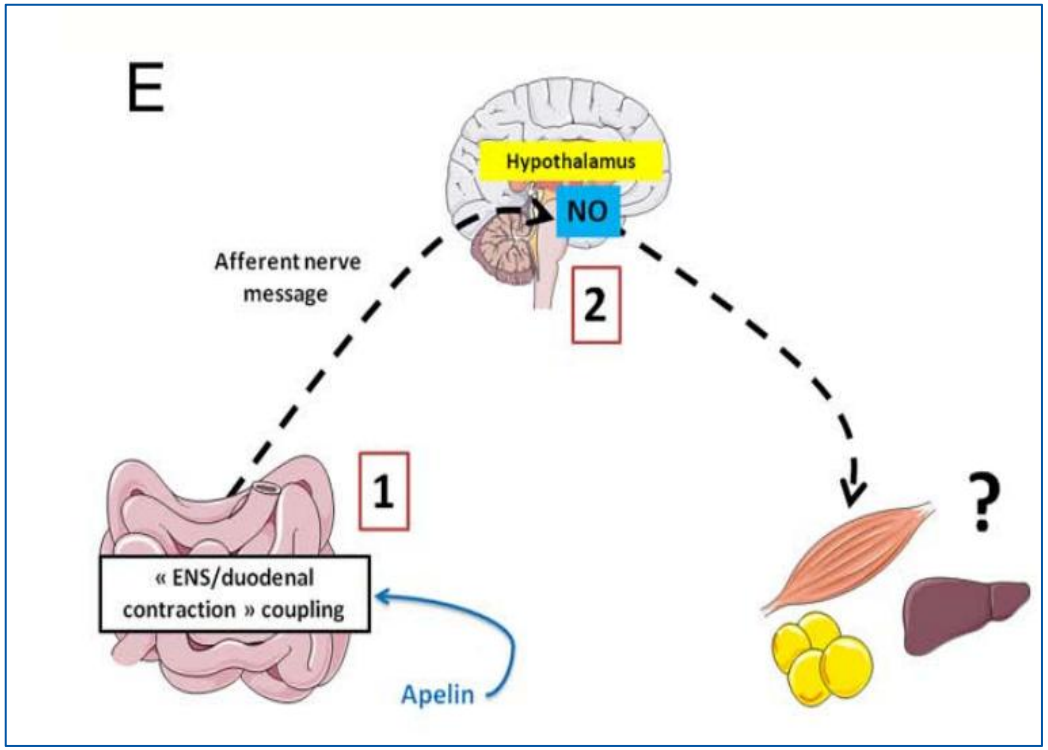
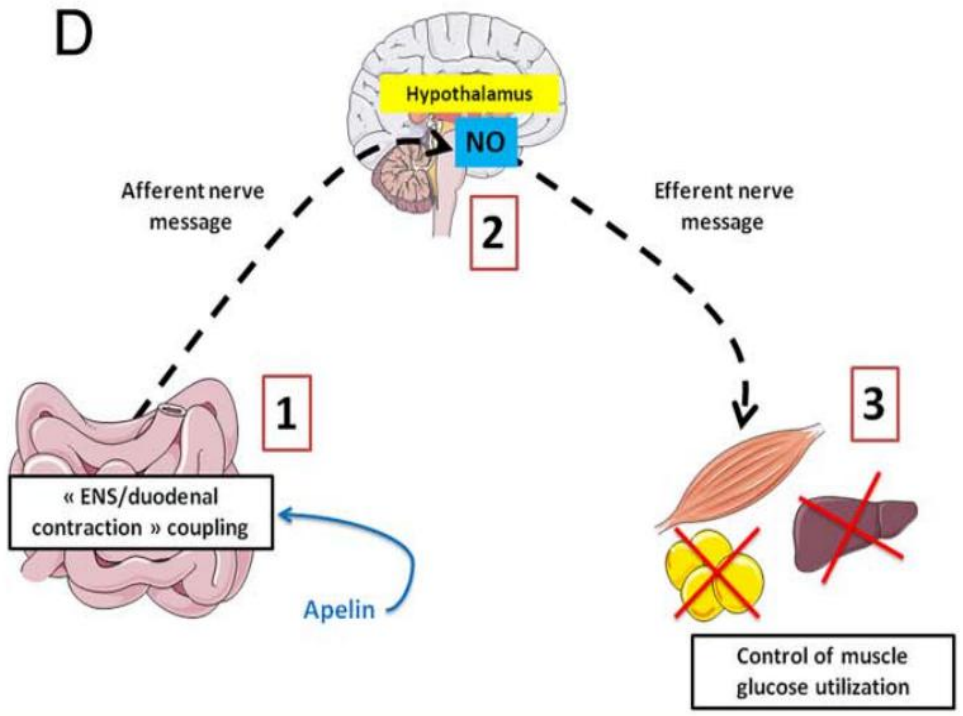


Figure 4E：结果示意图，apelin通过改变十二指肠的收缩，调控下丘脑释放NO

3. Duodenal apelin controls muscle glucose utilisation via hypothalamic NO



3. Duodenal apelin controls muscle glucose utilisation via hypothalamic NO

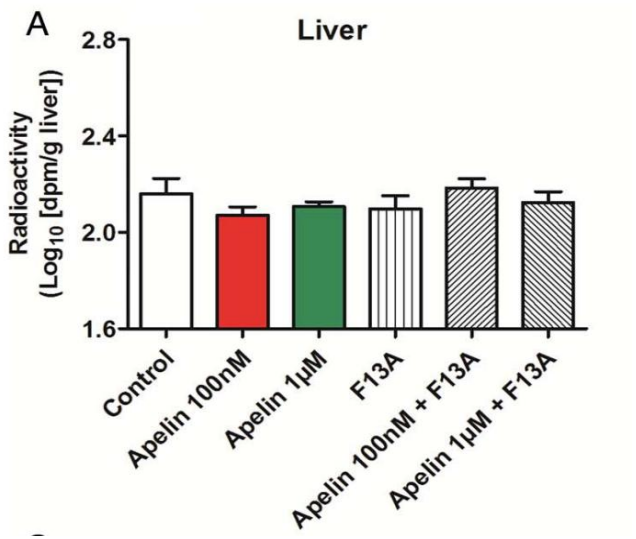
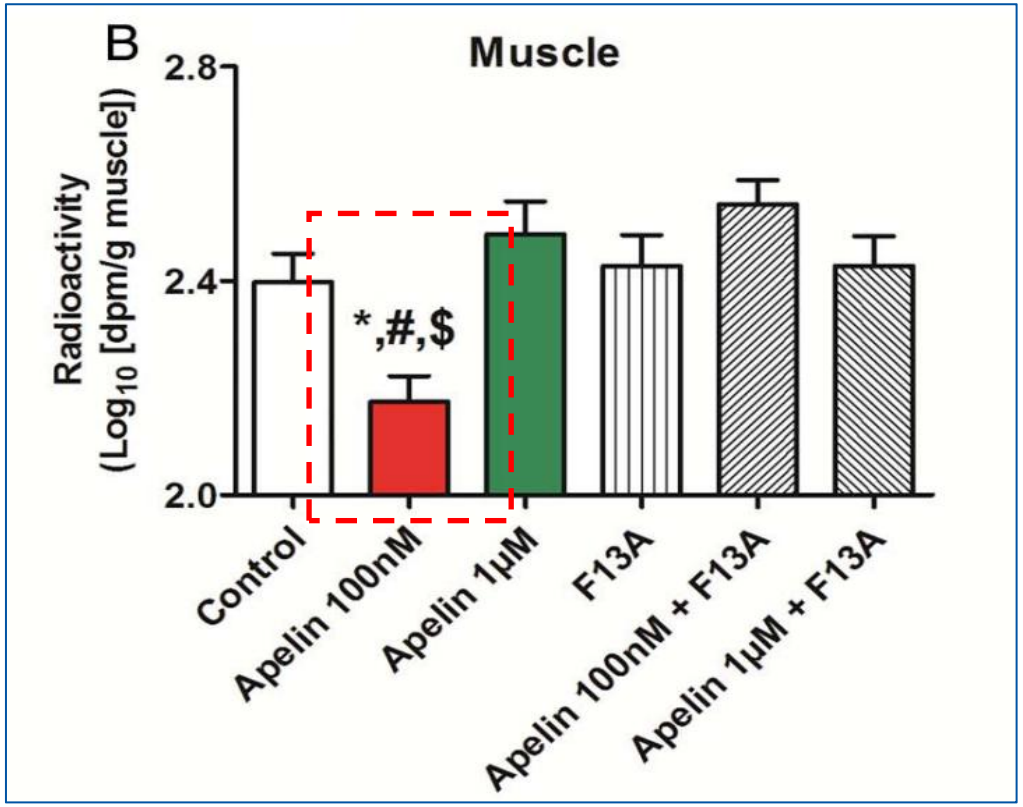


Fig 5A：肝脏



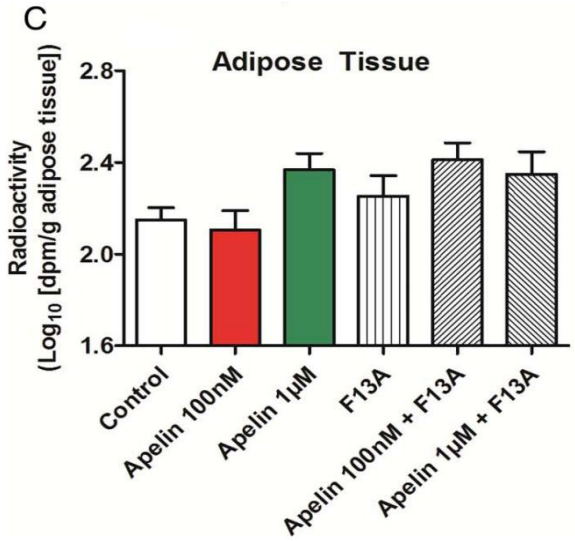


Fig 5C：脂肪组织

Fig 5B：十二指肠apelin调节肌肉葡萄糖的利用

3. Duodenal apelin controls muscle glucose utilisation via hypothalamic NO

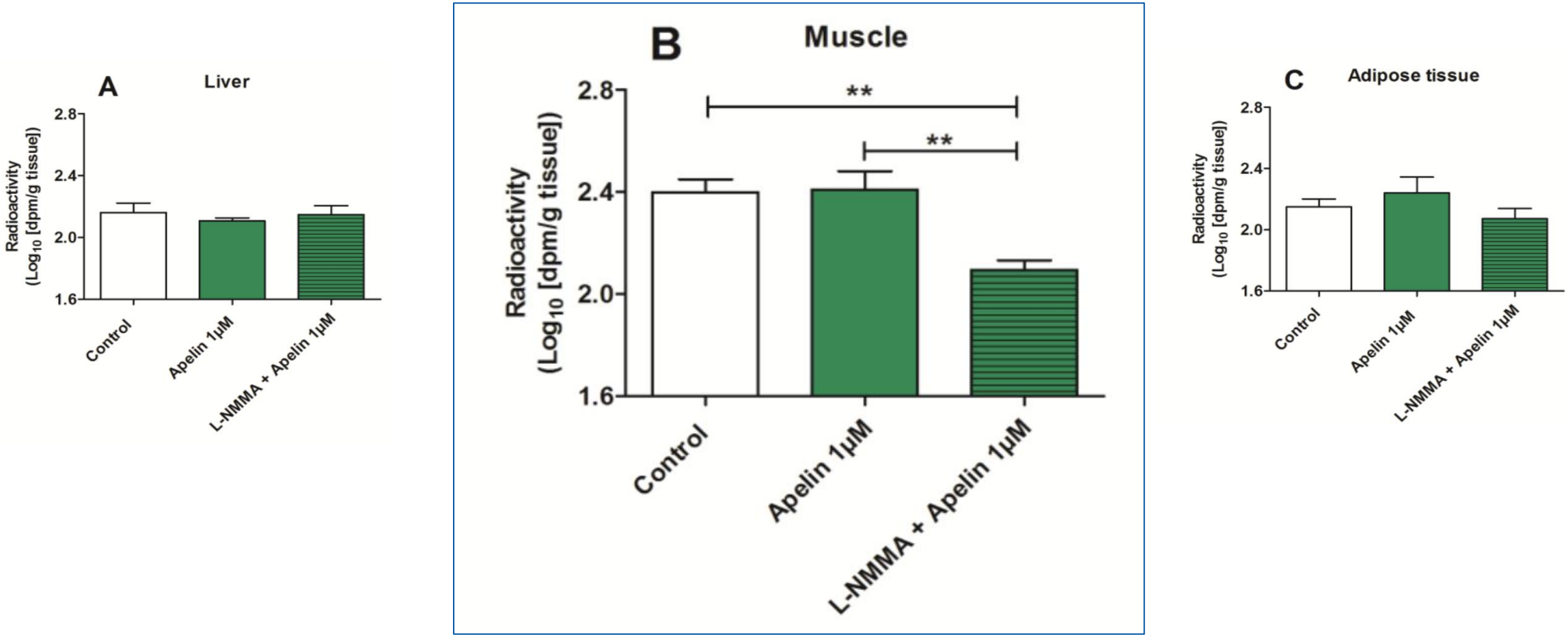


Figure S5：下丘脑NO介导 肠Apelin对肌肉葡萄糖利用的影响

3. Duodenal apelin controls muscle glucose utilisation via hypothalamic NO

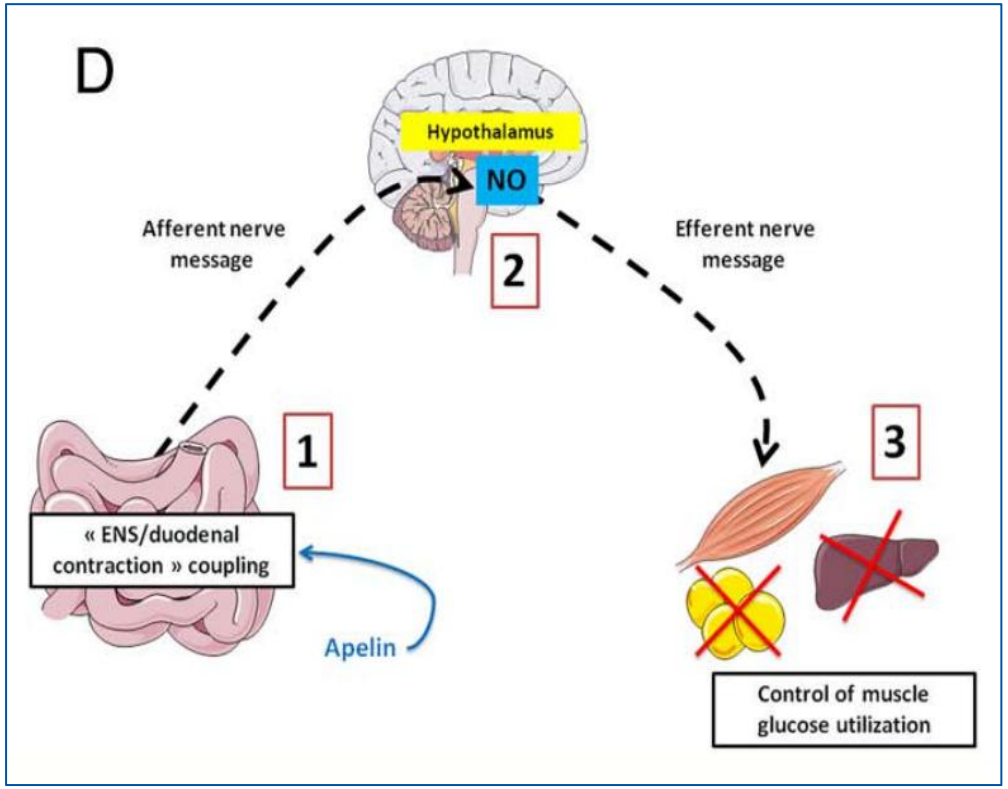


Figure 5D：结果示意图：十二指肠Apelin通过下丘脑传导，调控肌肉葡萄糖的利用。

4. Chronic apelin gavage increases glucose tolerance via a decrease in duodenal motility

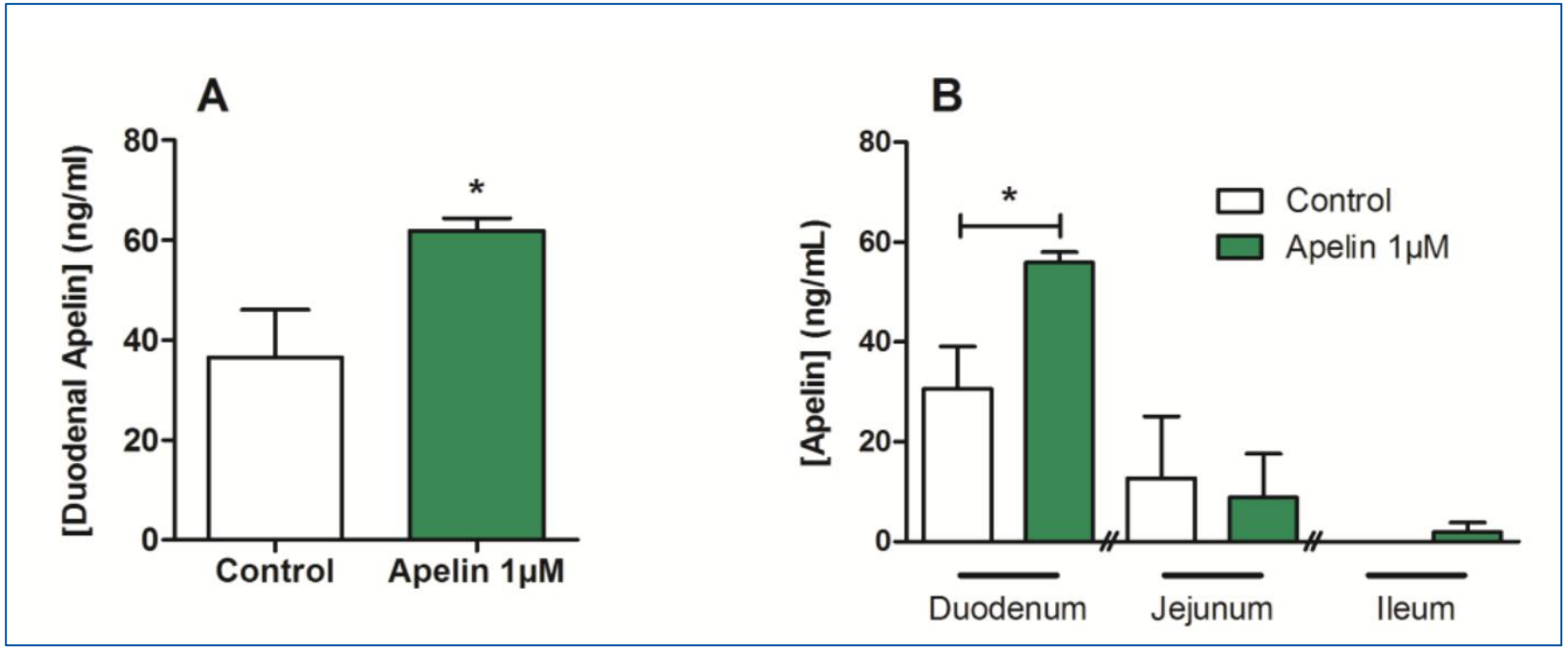


Figure S6A-B：十二指肠是apelin跨细胞转运的关键部位

4. Chronic apelin gavage increases glucose tolerance via a decrease in duodenal motility

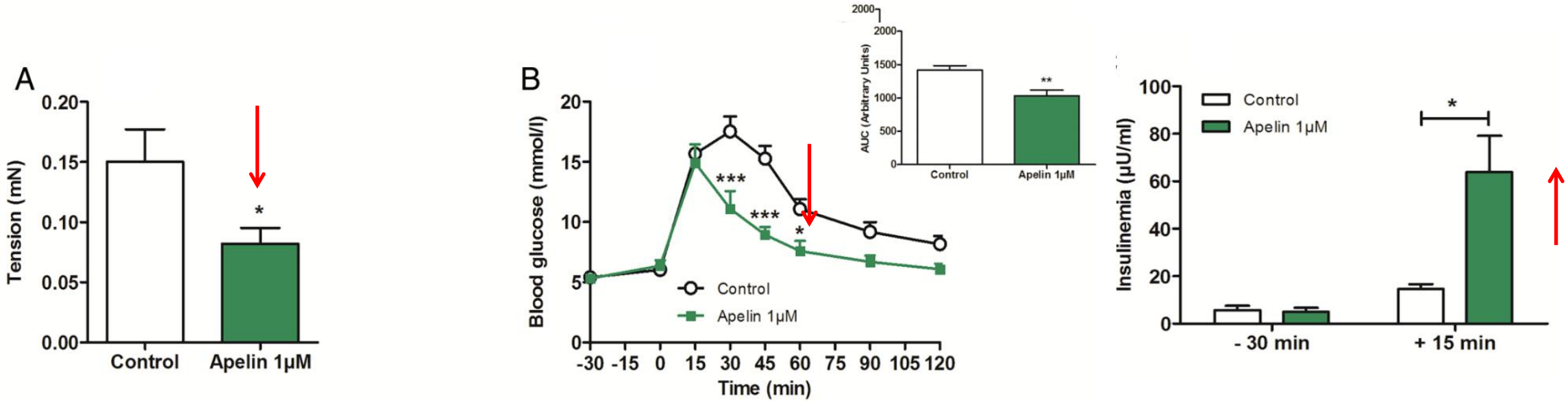
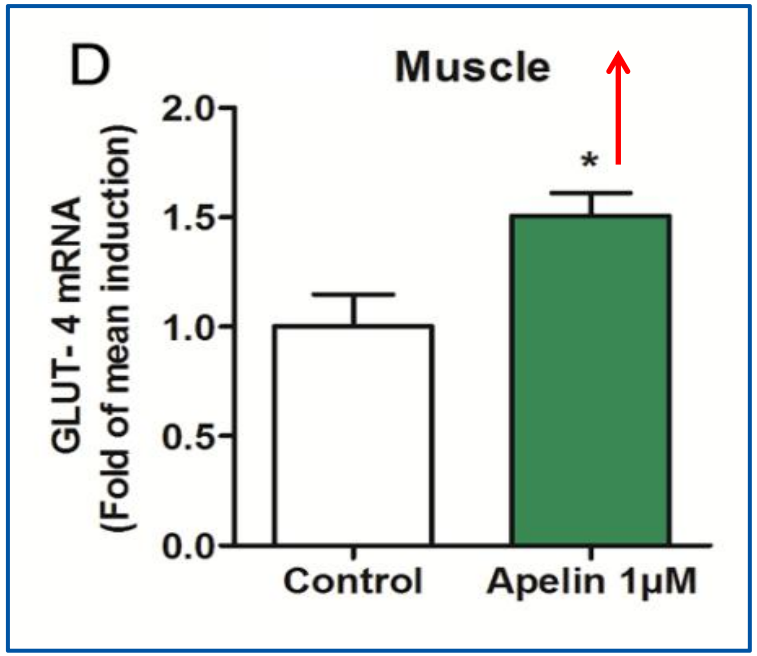
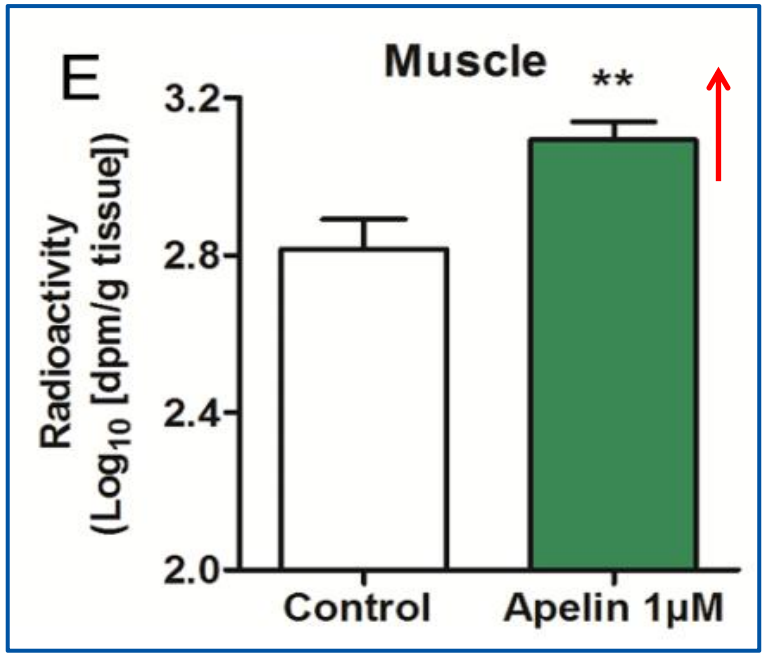
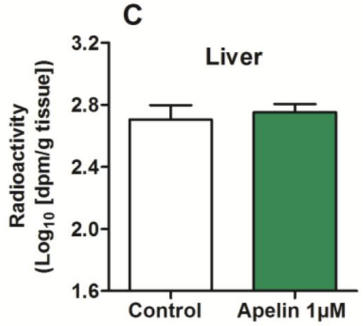


Figure 6A-C：慢性apelin给药降低十二指肠运动，提高葡萄糖耐受力和胰岛素释放

4. Chronic apelin gavage increases glucose tolerance via a decrease in duodenal motility







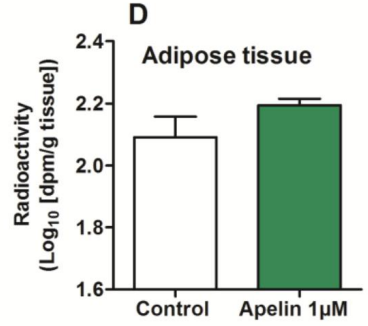


Figure 6D-E：慢性apelin给药 葡萄糖转运载体4型（GLUT4）mRNA表达和进入肌肉中的葡萄糖增加，肝脏和脂肪不明显

5. Apelin restores normal duodenal motility and improves glucose tolerance in obese/diabetic mice

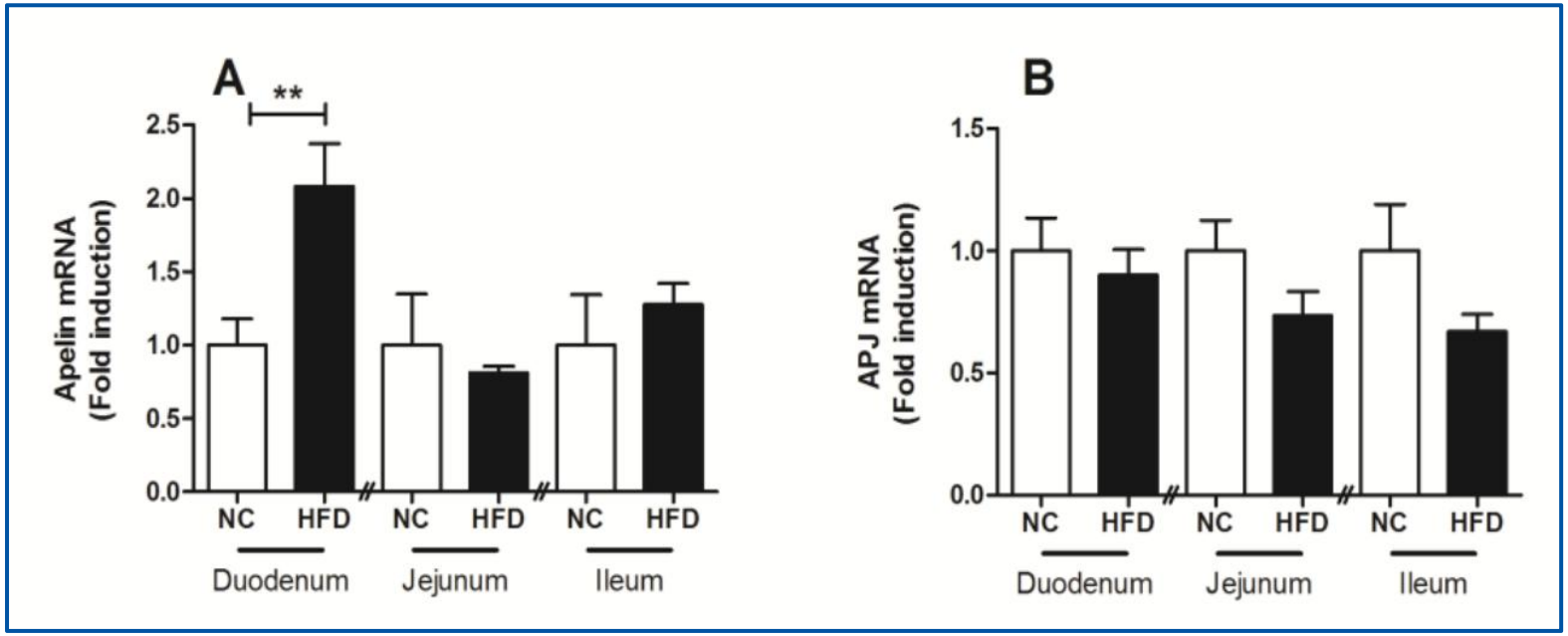


Figure S7：未处理/高脂饮食小鼠 Apelin（A）和APJ（B）mRNA在十二指肠、空肠与回肠中的表达。

5. Apelin restores normal duodenal motility and improves glucose tolerance in obese/diabetic mice

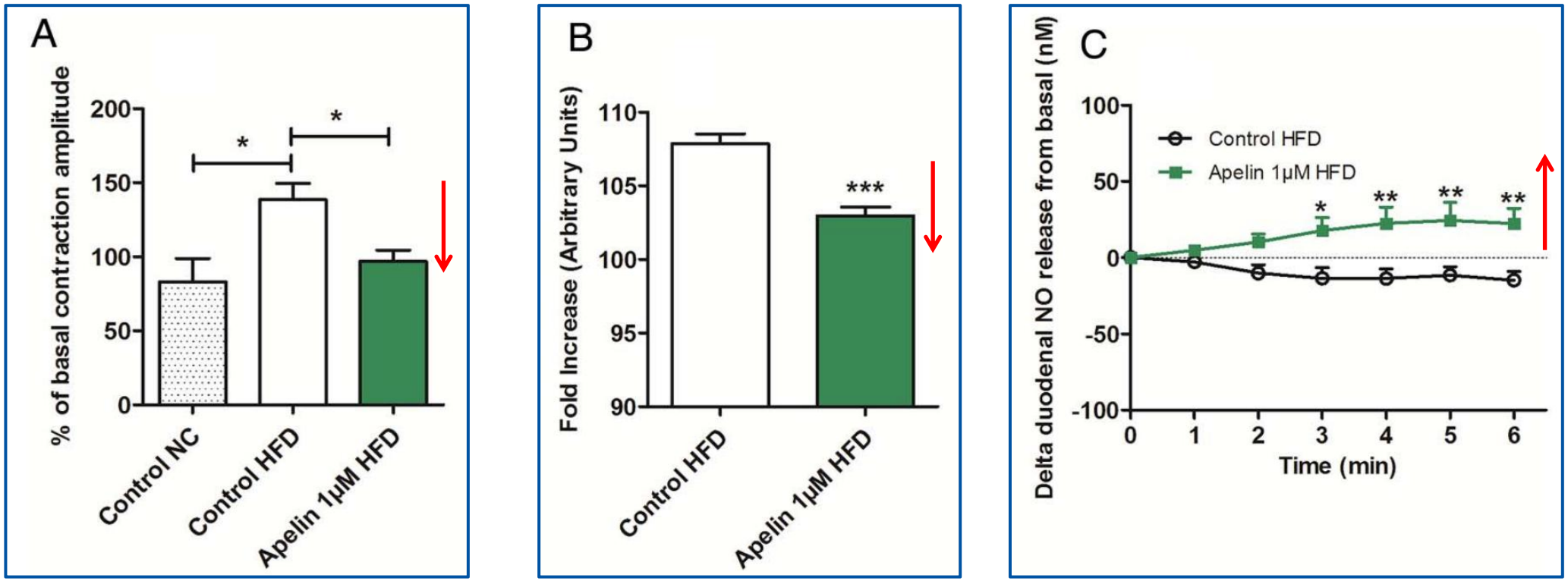


Figure 7A-C：未处理/高脂饮食小鼠急性Apelin 1μM下十二指肠收缩力（A）和电活动力（B）十二指肠NO释放（C）。

5. Apelin restores normal duodenal motility and improves glucose tolerance in obese/diabetic mice

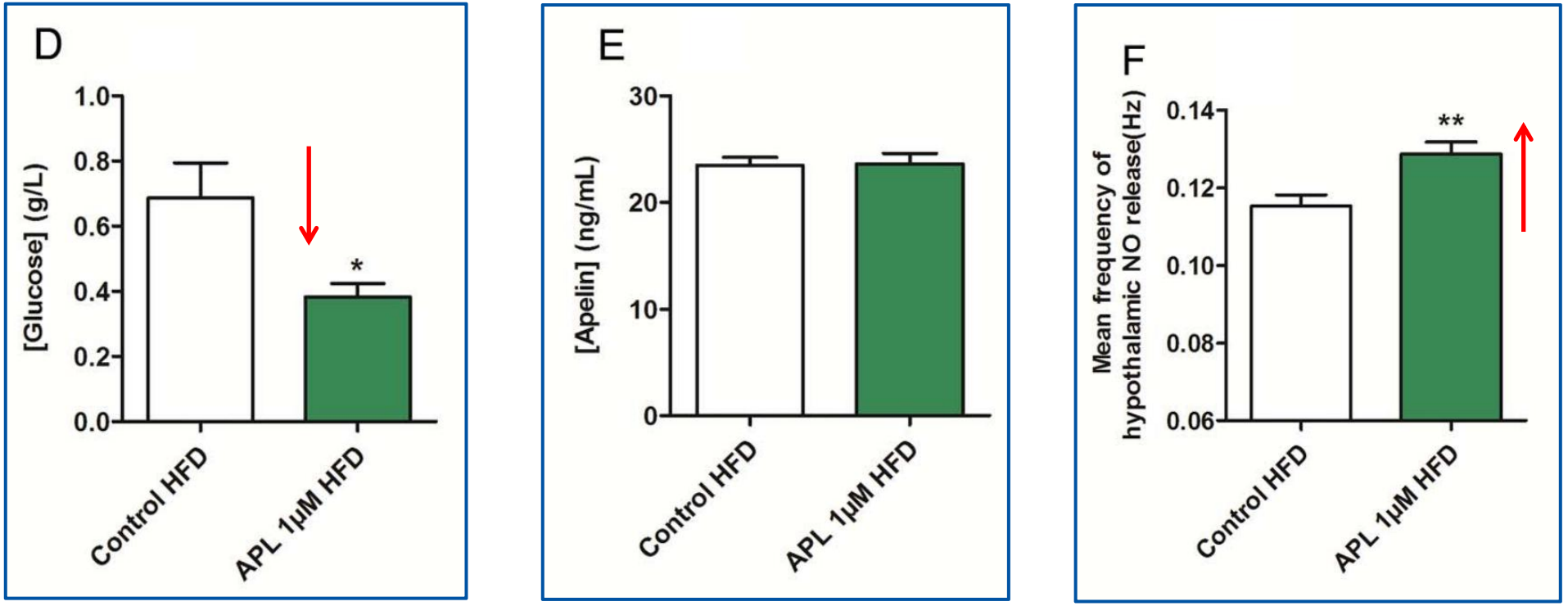


Figure 7D-F：未处理/高脂饮食小鼠 1μM Apelin 离体肠膜葡萄糖的吸收（D）和离体Apelin 的吸收（E）在体下丘脑NO释放（F）。

5. Apelin restores normal duodenal motility and improves glucose tolerance in obese/diabetic mice

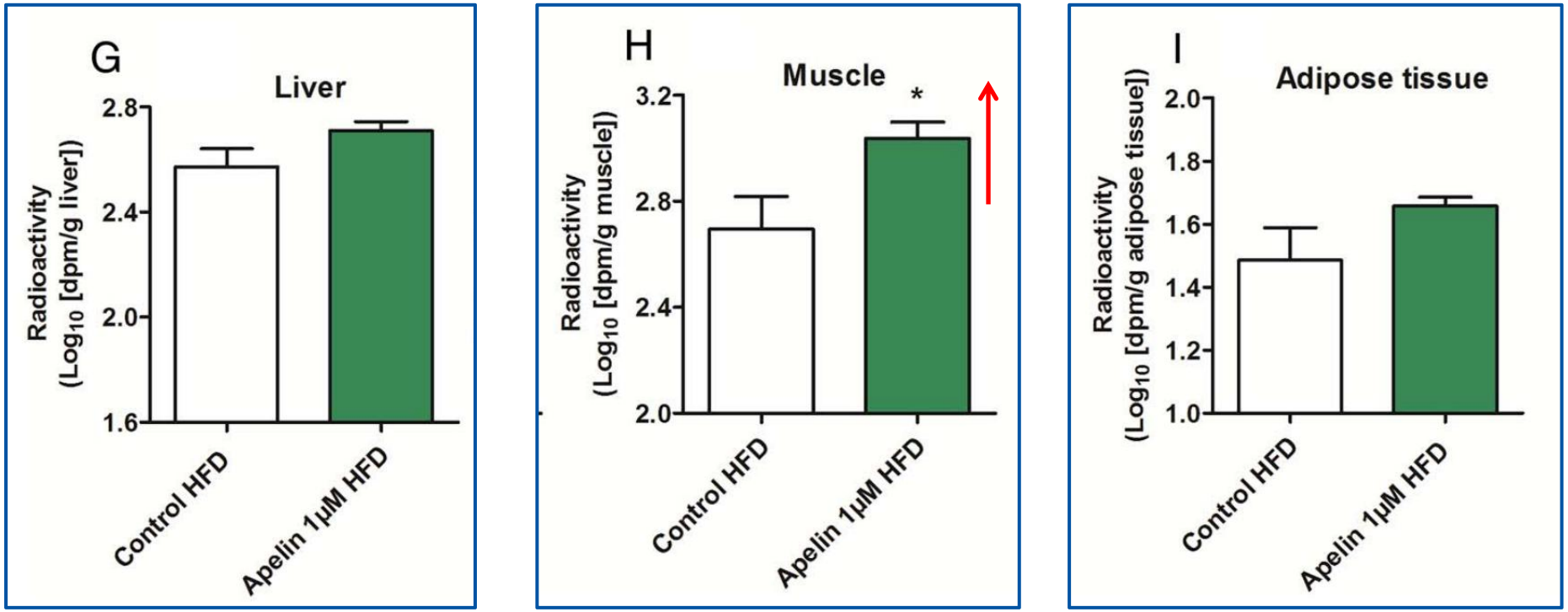


Figure 7G-I：口服放射性葡萄糖，在体测量葡萄糖进入肝脏（G），肌肉（H）和脂肪组织（I）的量

5. Apelin restores normal duodenal motility and improves glucose tolerance in obese/diabetic mice

A

Parameters	NC	HFD	HFD APL1µM	Statistics (NC vs HFD)	Statistics (HFD vs HFD APL 1µM)
Weight (g)	25,23 ± 0,87	46,23 ± 0,91	45,70 ± 0,47	***	ns
Fasted glucose (mmol/L)	5,40 ± 0,20	12,72 ± 0,86	11,14 ± 0,30	***	ns
Fed glucose (mmol/L)	8,56 ± 0,21	11,34 ± 0,35	9,66 ± 0,65	***	p = 0 ,0588
Fasted insulin (mU/L)	5,82 ± 1,85	65,41 ± 10,93	29,43 ± 9,01	***	*
HOMA-IR	1,37 ± 0,43	41,56 ± 7, 29	15,05 ± 4,86	***	*

Figure 8A：高脂饮食（HFD）小鼠，口服给药1周（H2O/ Apelin 1µM）对代谢参数的影响。

5. Apelin restores normal duodenal motility and improves glucose tolerance in obese/diabetic mice

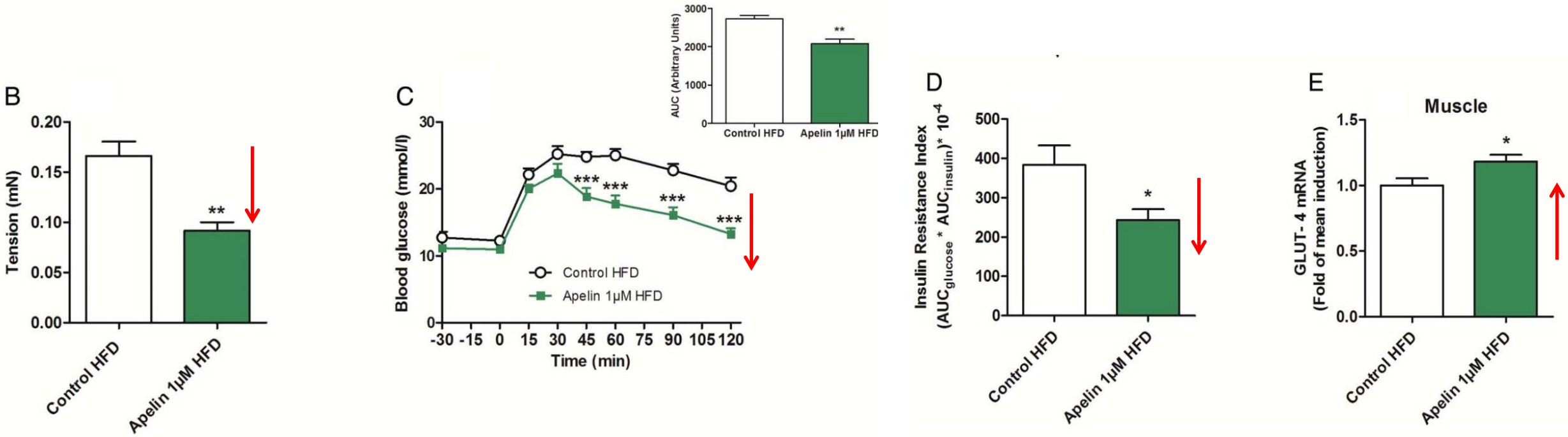


Figure 8B-E：高脂饮食（HFD）小鼠，口服给药1周（H2O/ Apelin 1μM）降低十二指肠收缩（B），改善糖耐量（C）和胰岛素抵抗（D），增加肌肉中GLUT4 mRNA的表达（E）。

PART FOUR

讨论

思考

01

apelin在肠神经系统中和在中枢神经系统中一样发挥着双重作用。十二指肠对于apelin的反应是具有剂量依赖性的。

02

肠道神经中枢神经元是apelin作用于十二指肠运动的靶器官。

思考

03

通过下丘脑的传导，十二指肠的收缩能够控制外周葡萄糖利用率。

04

慢性口服Apelin能够改善高脂饮食小鼠葡萄糖耐量和胰岛素抵抗。因此，将肠道神经系统(ENS)神经元作为靶器官,通过apelin 调节肠道收缩来降低十二指肠的运动，这作为一种治疗2型糖尿病合并症（如高血糖和胰岛素抵抗）的新的治疗方法具有实际的潜在的价值。

PART FIVE

结论

结论

在生理条件下，ENS、十二指肠收缩和大脑之间的相互作用对于控制葡萄糖利用率是至关重要的。肠道Apelin是在这个系统中扮演一个关键角色。

PART SIX

思考与启发

思考与启发

01

大胆假设，小心求证。验证各组织之间的互作作用，起关键作用的因子，及其作用的机制和通路。

02

本研究中的试验方法和实验设计思路(层层递进，正反论证)值得借鉴，在鱼类的研究中可以参考。

03

论文写作调理清楚，层层递进，简明扼要。多采用，为了检验……，我们测定了……，首先,其次……，结果表明……，更论证了……。

THANKS