读书报告

汇报人：胡俊仪

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Acta Physiologica

Acta Physiol 2010, 198, 335–348

REVIEW

Role of orexin in the regulation of glucose homeostasis

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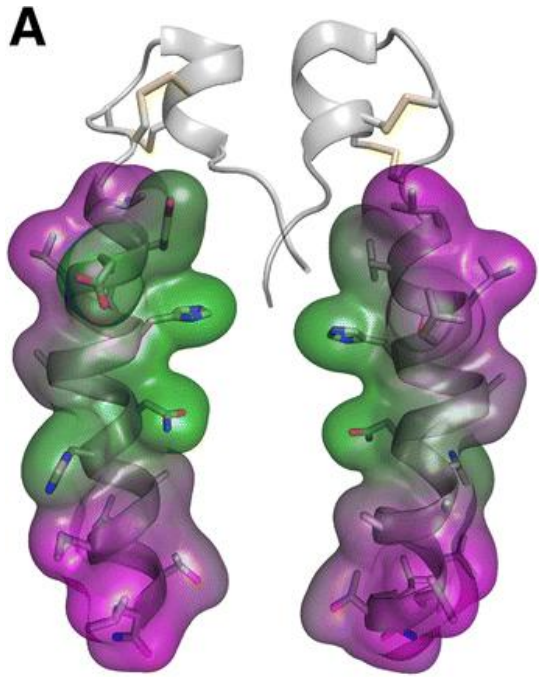
食欲素在调节葡萄糖平衡中的作用

河南师范大学水产学院 College of Fisheries Henan Normal University

Orexin

Orexin 的发现

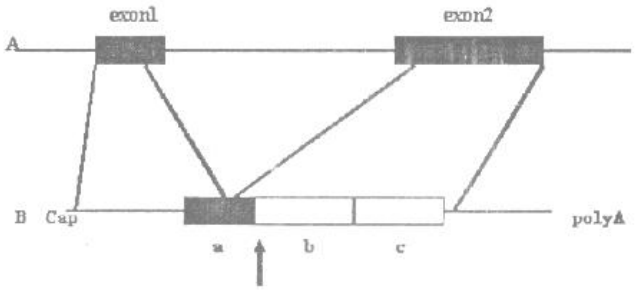


Orexin-A peptide

1998年Yanagi sawa 等在寻找G蛋白受体相连结的配体时，在下丘脑侧部偶然发现2种与食欲有关的神经肽orexinA和orexinB 。

Orexin

Orexin 的基因结构及分布



A: genome of prepro – orexin

B: mRNA of prepro – orexin

a: mRNA of Signal sequence

b: mRNA of orexinA

c: mRNA of orexinB

↑: Site where signal peptide will be cut

Fig1 Gene structure of prepro – orexin

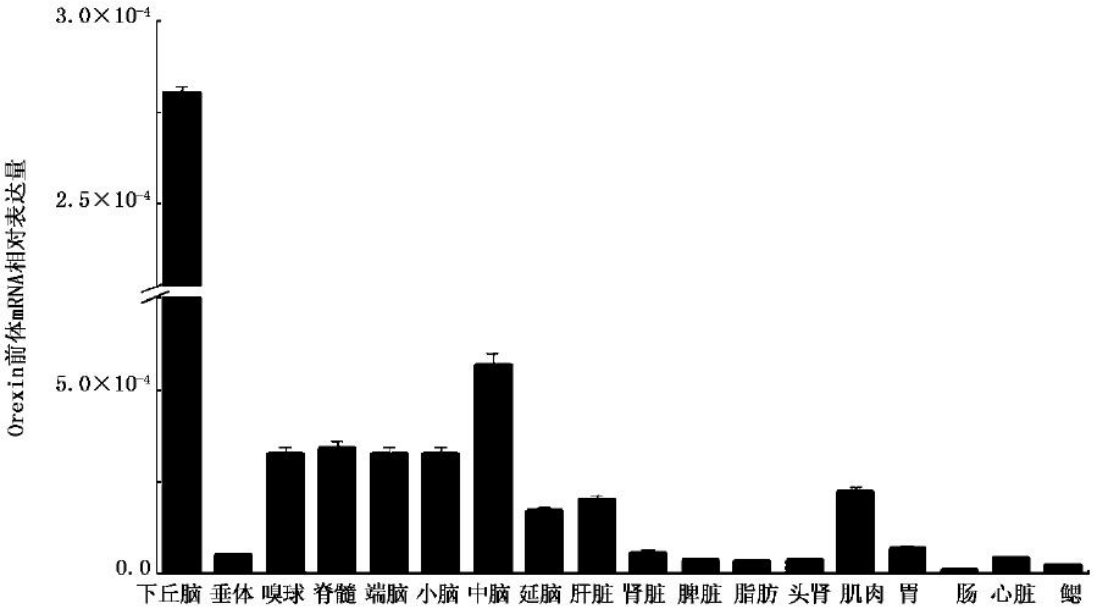
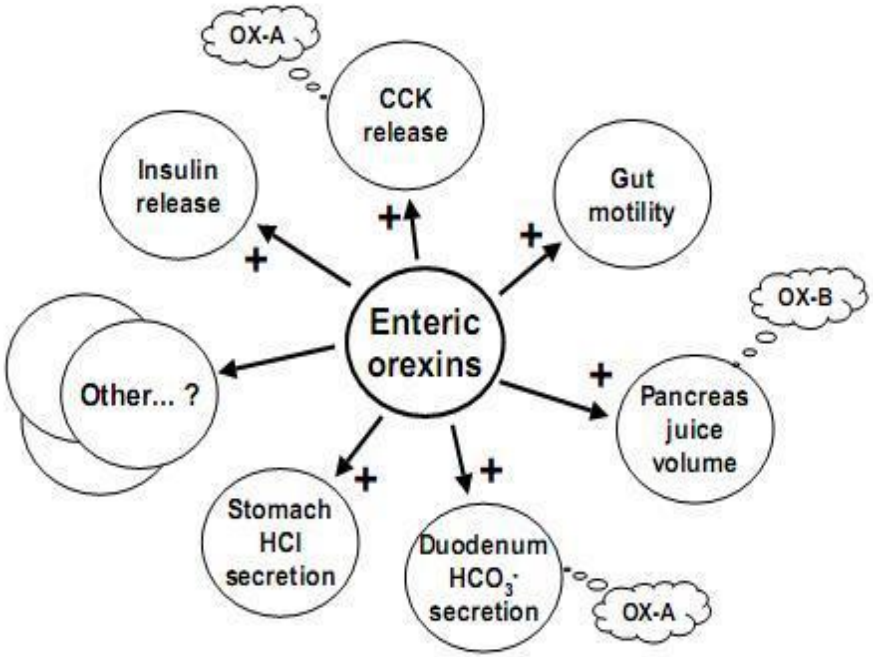


图3 尼罗罗非鱼 Orexin 前体基因在不同组织中的表达(引自 陈文波等,2011[13])

Orexin

Orexin 的功能

- Orexin食欲肽是一种由下丘脑分泌的神经肽，广泛分布于脊椎动物的中枢神经系统以及外周组织，Orexin 通过其受体发挥作用，参与机体摄食、能量稳态、体温、睡眠、觉醒周期、生殖、内脏活动和内分泌等方面的调节（Adamantidis & de Lecea, 2008）。



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1 Regulation of food intake

最早在LHA和弯隆周围核中发现orexin表达神经元，而LHA和弯隆周围核被认为是摄食管理中心。因此最早认为orexin的作用是促进摄食。

1 Regulation of food intake

Genetic Ablation … Results in Narcolepsy, Hyp…

Junko Hara,Carsten T… 54, May, 2001 by Cell Press

To ea… regulation of feedi…

Willie… Yanagisawa, M.200…

orexin 敲除小鼠和

orexin神经元缺陷小鼠

摄食减少

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1 Regulation of food intake

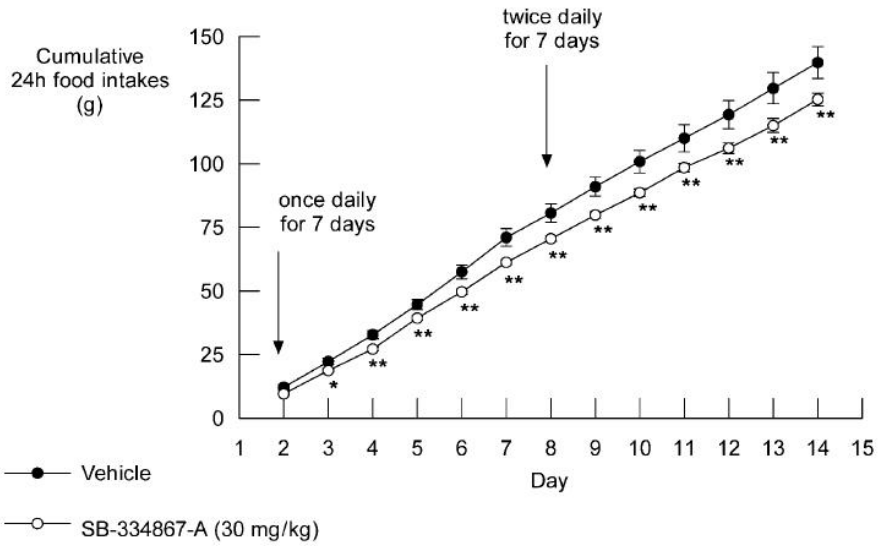
ELSEVIER

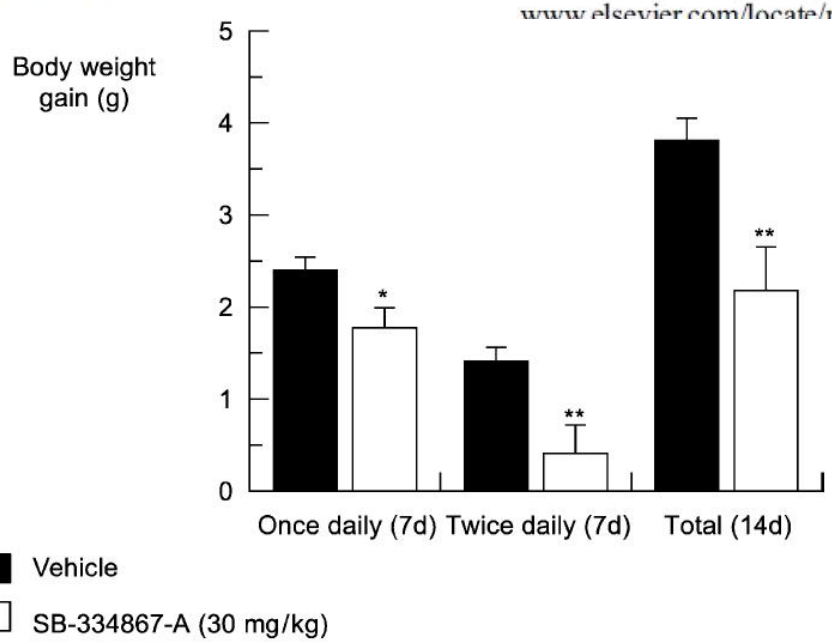
REGULATORY PEPTIDES

www.elsevier.com/locate/regpep

Anorectic, thermogenic and anti-obesity activity of a selective orexin-1 receptor antagonist in *ob/ob* mice

Andrea C. Haynes [a,*], Helen Chapman [a], Colleen Taylor [a], Gary B.T. Moore [a], Michael A. Cawthorne [b], Mohammad Tadayyon [a], John C. Clapham [a], Jonathan R.S. Arch [a]



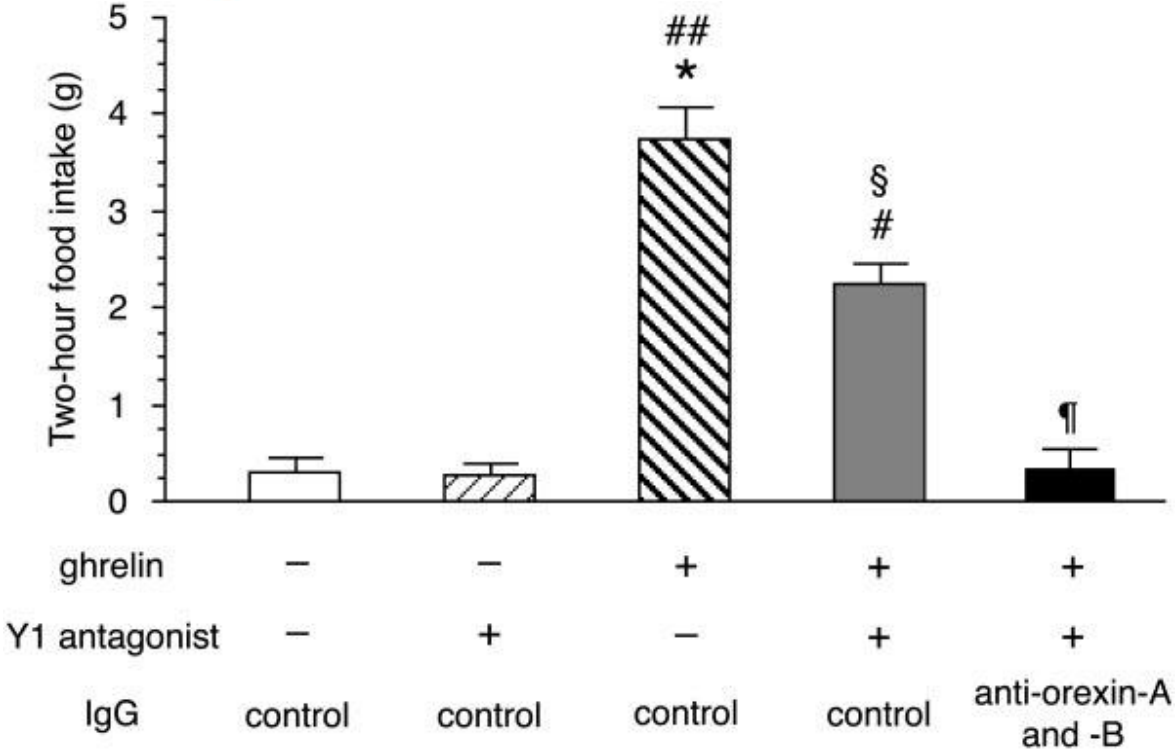


OX1R a… …ces food intake and body we… …ynes et al. 2002).

Orexin 通过其受体发挥作用

1 Regulation of food intake

Ghrelin-Induced Food Intake Is Mediated via the Orexin Pathway



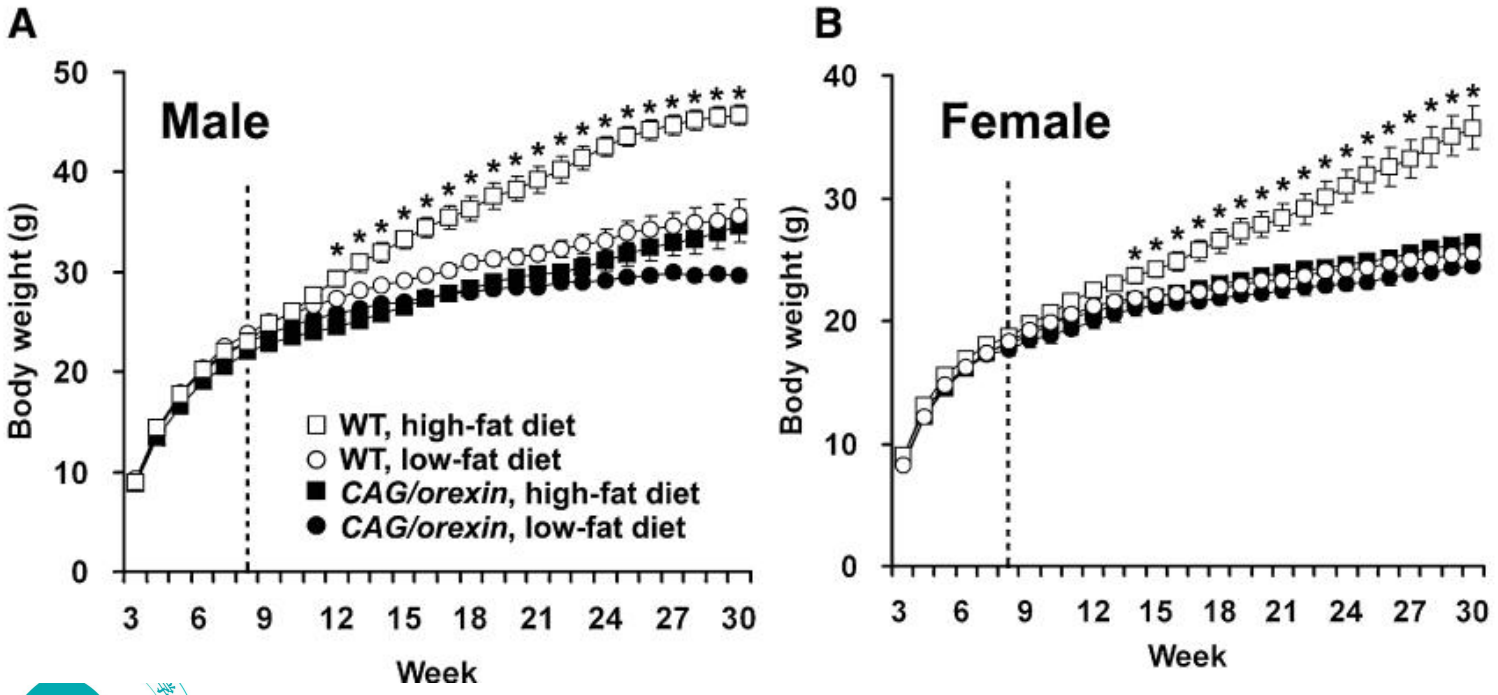
Food intake induced by ghrelin, a peptide produced in the stomach and hypothalamus, is partly mediated via the orexin pathway (Toshinai et al. 2003).

1 Regulation of food intake

Cell PRESS

Enhanced Orexin Receptor-2 Signaling Prevents Diet-Induced Obesity and Improves Leptin Sensitivity

Hiromasa Funato,[1,7] Allen L. Tsai,[1,7] Jon T. Willie,[1,4] Yasushi Kisanuki,[1] S. Clay Williams,[1,2] Takeshi Sakurai,[3,5,6] and Masashi Yanagisawa[1,2,3,*]



Orexin selective agonist suppresses food intake in mice fed on high-fat diet, but not low-fat diet (Funato et al. 2009)

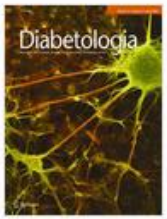
小结

a orexin stimulates food intake.

b orexin's activities via the activation of orexin-1 receptor or orexin-2 receptor.

c orexin increases or decreases food intake depending on plasma fuel levels to maintain energy homeostasis.

2 Regulation of glucose metabolism by orexin



Diabetologia
April 2008, Volume 51, Issue 4, pp 657–667

Age-related insulin resistance in hypothalamus and peripheral tissues of orexin knockout mice

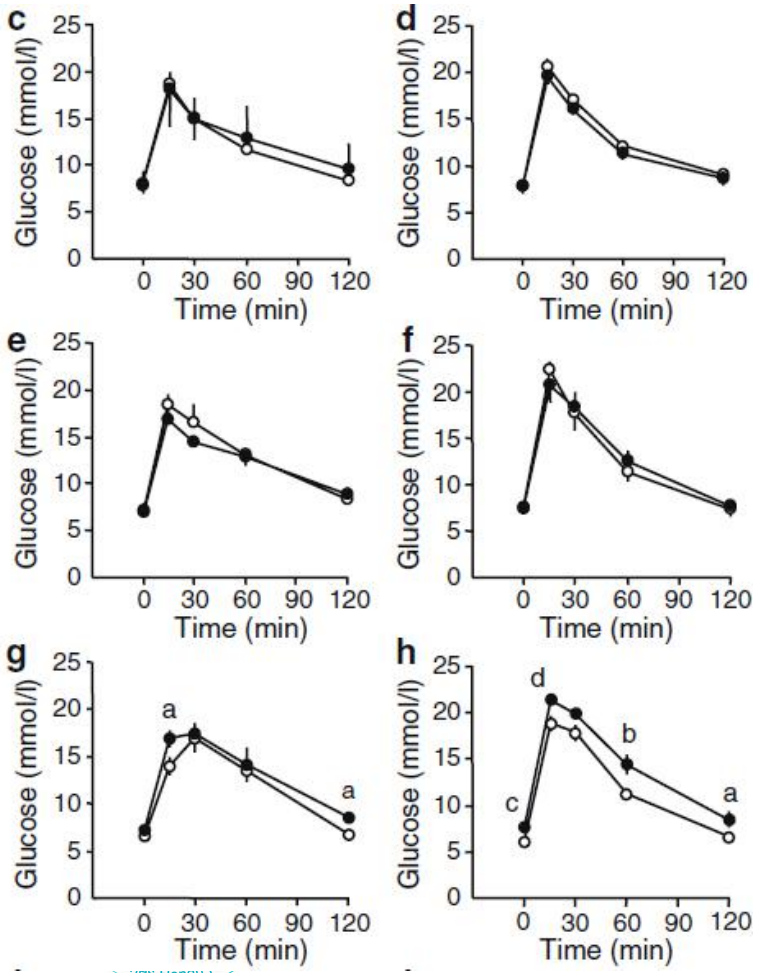


Fig. 1 Age-related deterioration in glucose tolerance in orexin knockout mice.Male (c) and female (d) mice at 2 months of age, male (e) and female(f) mice at 6 months of age, and male (g) and female (h) mice at9 months of age were fasted for 10 h.

orexin deficiency causes an age-related development of impaired glucose tolerance and insulin resistance in both male mice without obesity and female mice.(Tsuneki et al. 2008)

2 Regulation of glucose metabolism by orexin

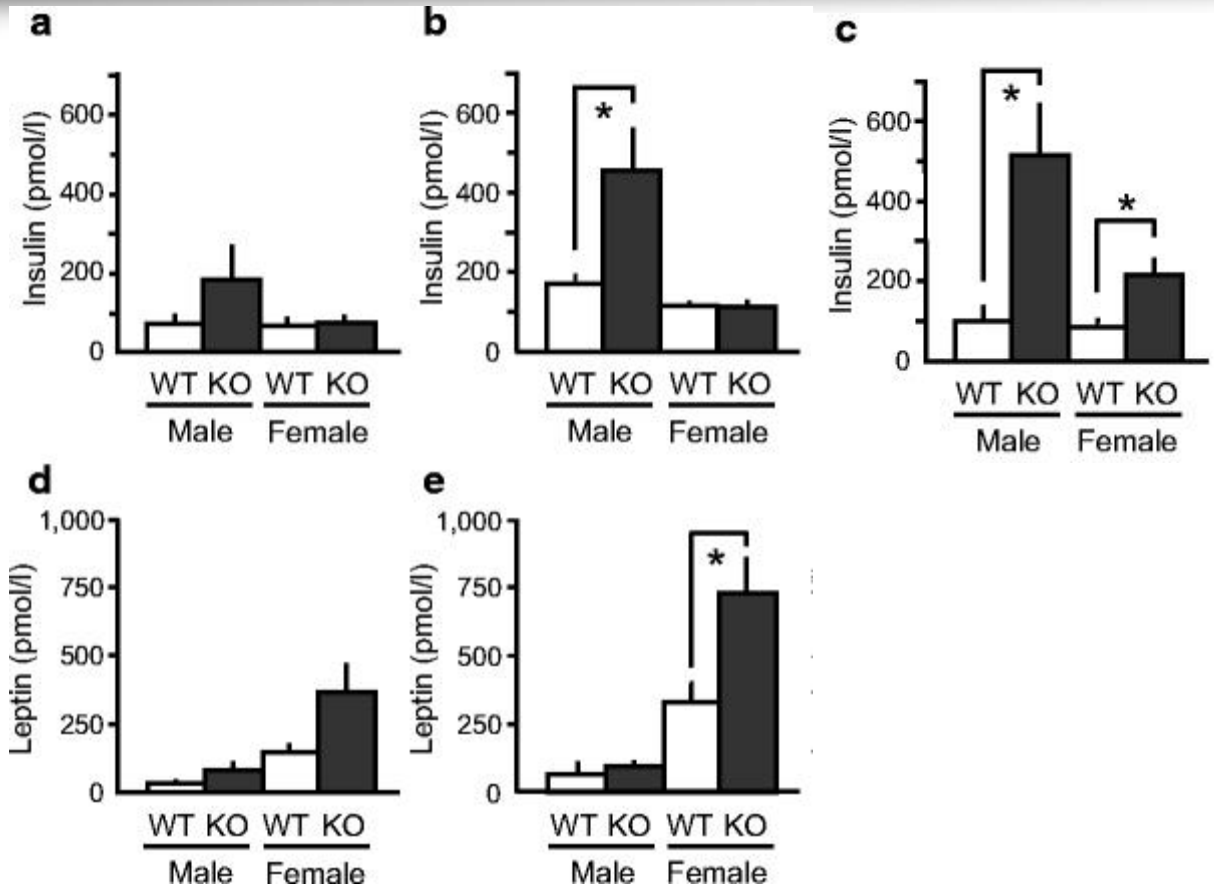
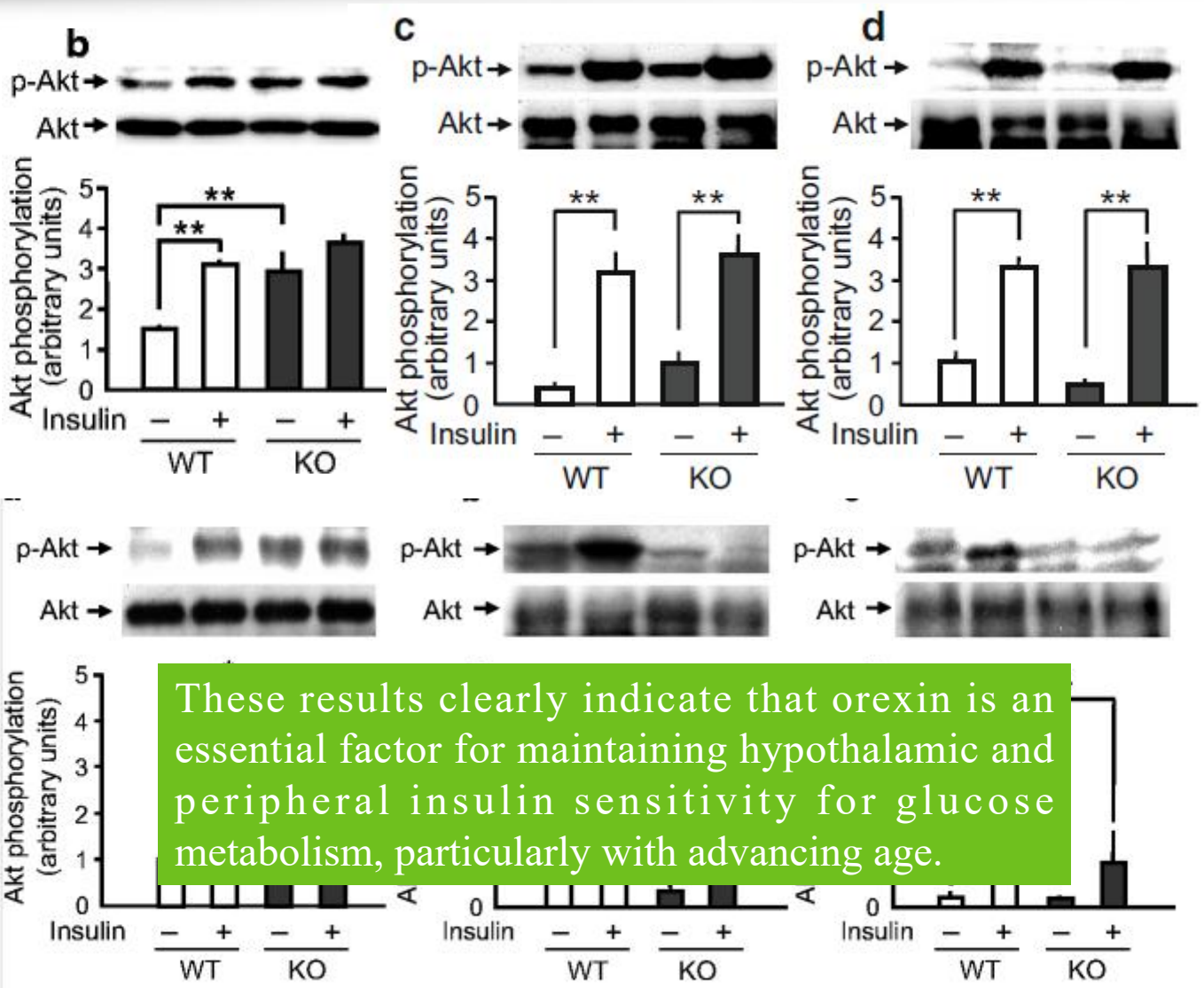


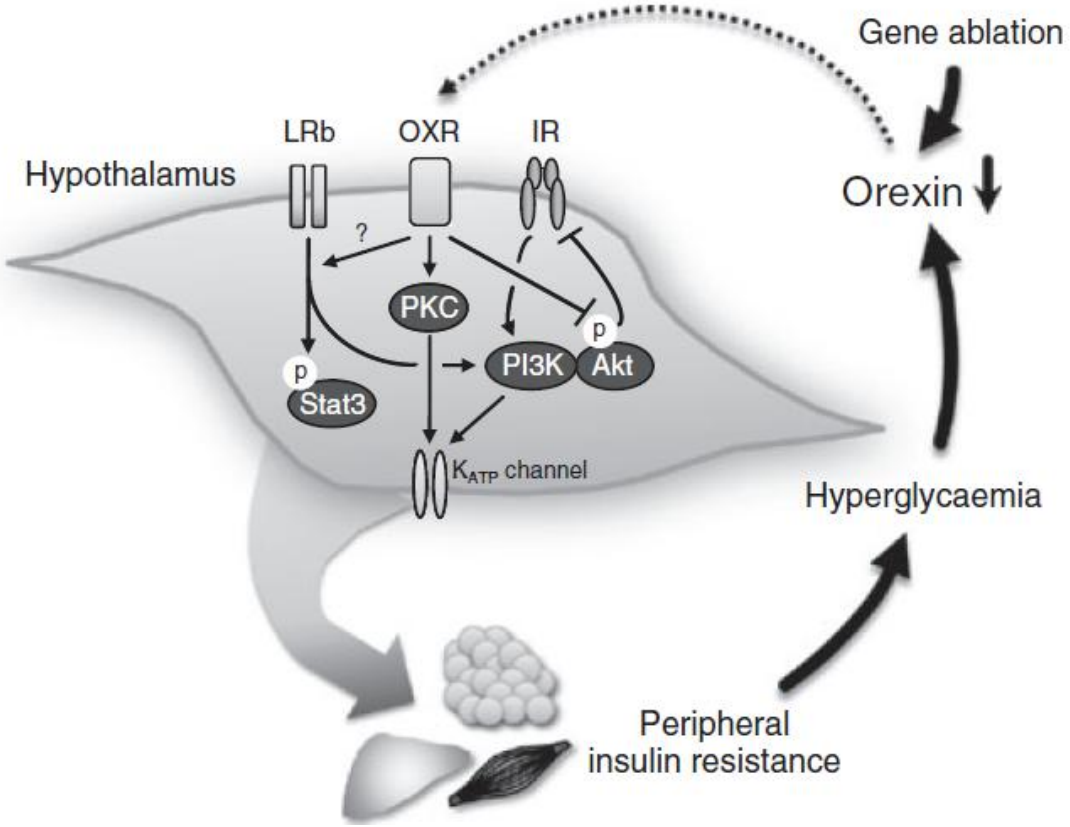
Fig. 3 Age-related changes in serum levels of insulin and leptin in orexin knockout mice. a–c Serum insulin levels in mice at 2 months (a), 6 months (b) and 9 months of age (c) on an NCD. d, e Serum leptin levels in mice at 2 months (d) and 9 months of age (e)

2 Regulation of glucose metabolism by orexin



These results clearly indicate that orexin is an essential factor for maintaining hypothalamic and peripheral insulin sensitivity for glucose metabolism, particularly with advancing age.

2 Regulation of glucose metabolism by orexin



示意图表示涉及食欲素缺乏在胰岛素抵抗和瘦素抵抗发展中的恶性循环。

小结

1.食欲素是维持外周胰岛素对葡萄糖代谢敏感性的一个重要因素，特别是随着年龄的增长。

2.食欲素通过激活K_{ATP}通道来增强胰岛素的作用，抑制肝糖原的产生。

3 Functions of orexin in the peripheral tissues

orexin 在外周组织中的功能

orexin及其受体广泛存在于外周器官，表达细胞主要为内分泌细胞，如胸交感干神经节、胃、肠、胰腺、肾脏、肾上腺、胎盘、睾丸、附睾等。

orexin 神经元通过响应外周血液葡萄糖、瘦素以及胃饥饿素的代谢信号能直接感受机体的营养状况。

3 Functions of orexin in the peripheral tissues

最先在豚鼠的肠道中发现了类食欲素的免疫反应活性和功能性食欲蛋白受体。（Orexin synthesis and response in the gut.Kirchgessner, A.L. & Liu, M. 1999.Neuron 24, 941–951.）

食欲素A的神经内分泌功能最初在肠内分泌细胞系STC-1细胞中表现。（The STC-1 cells express functional orexin-A receptors coupled to CCK release.Larsson et al.2003.Biochem Biophys Res Commun 309,209–216.）

在人类肠道中也发现了Orexin-A和食欲素受体的免疫反应活性。(Ehrstrom et al. 2005).

3 Functions of orexin in the peripheral tissues

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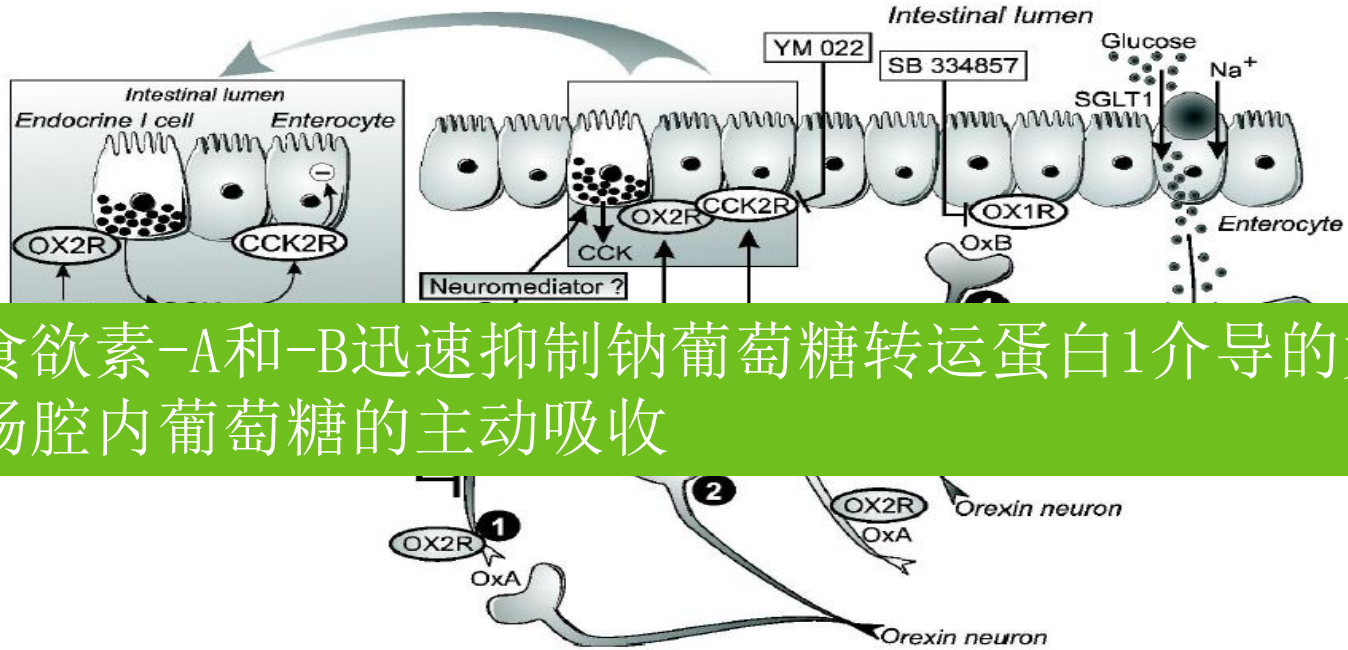
diabetes
A JOURNAL OF THE AMERICAN DIABETES ASSOCIATION

Orexins control intestinal glucose transport by distinct neuronal, endocrine and direct epithelial pathways



食欲素-A和-B迅速抑制钠葡萄糖转运蛋白1介导的大鼠肠腔内葡萄糖的主动吸收

Figure 8. Schematic drawing of inhibitory pathways involved in OxA and OxB inhibition of glucose absorption by enterocyte.

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3 Functions of orexin in the peripheral tissues

然而，仍然有一些论据反对小鼠和人类肠神经组织中食欲素生成细胞的存在。

ELSEVIER

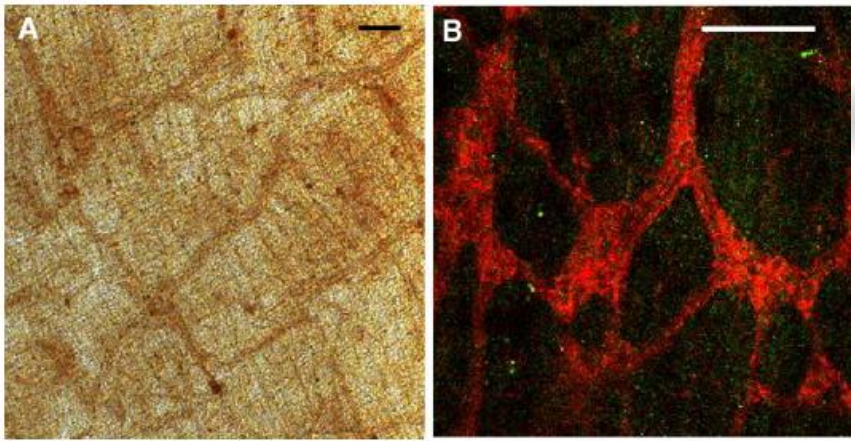
Regulatory Peptides

Volume 147, Issues 1–3, 10 April 2008, Pages 1-3

Rapid communication

Do enteric neurons make hypocretin? ☆

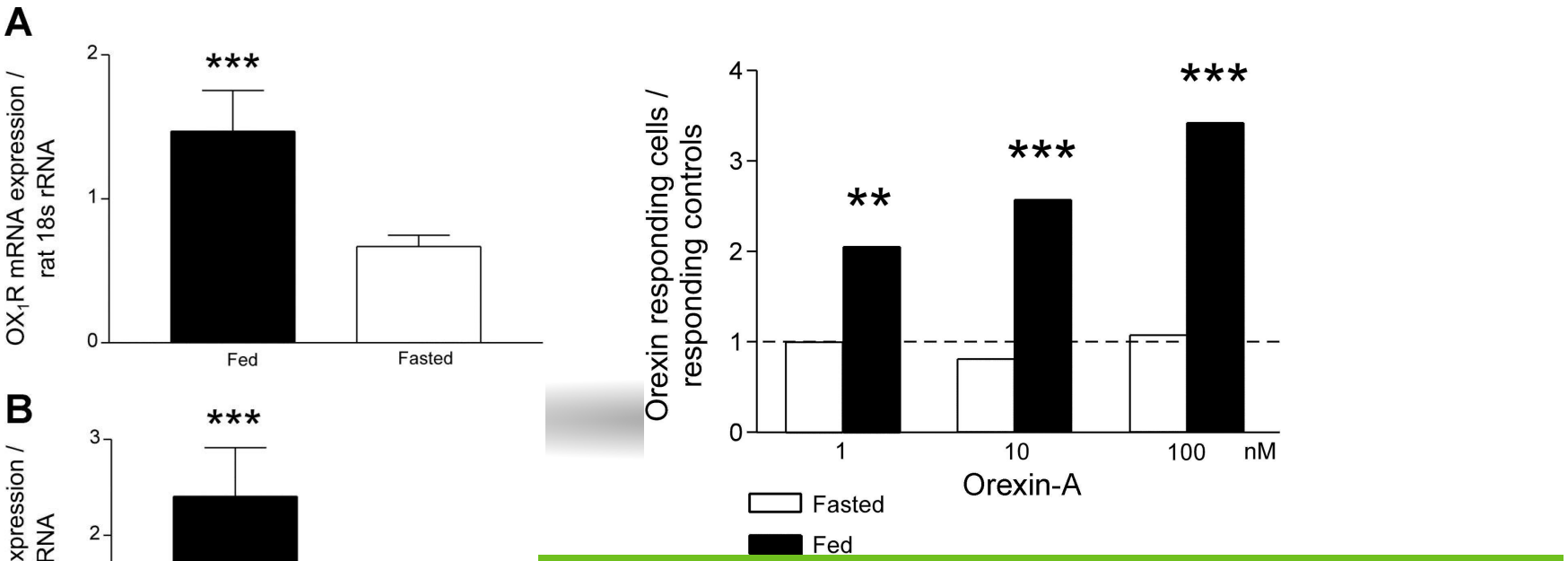
Christian R. Baumann [a, c], Erika L. Clark [a], Nigel P. Pedersen [a, d], Jonathan L. Hecht [b], Thomas E. Scammell [a]



3 Functions of orexin in the peripheral tissues

AMERICAN JOURNAL of PHYSIOLOGY
Gastrointestinal and Liver Physiology
American Physiological Society

Short food deprivation inhibits orexin receptor 1 expression and orexin-A induced intracellular calcium signaling in acutely isolated duodenal enterocytes(Bengtsson et al. 2009).



It should be noted that responsiveness to orexin-A in the gut appears to be modulated by food intake

小结

orexin 在肠中的作用

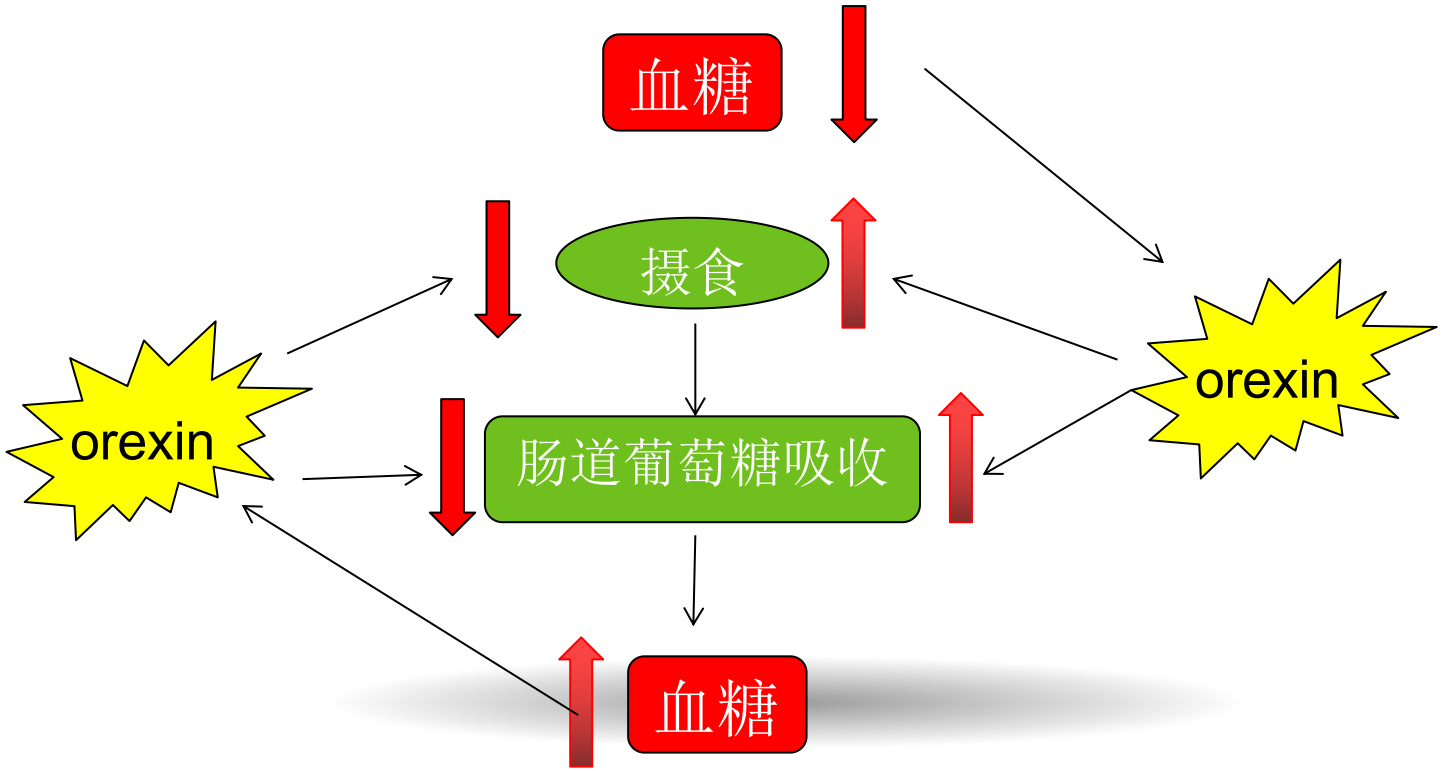
1

内源性食欲素直接调节肠内葡萄糖的吸收。但是，仍然有一些论据反对小鼠和人类肠神经组织中食欲素生成细胞的存在。

2

食欲素A在肠道中的功能似乎受食物摄入的调节。

总结



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