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学 位 论 文

**大鼠下丘脑腹外侧视前区和结节乳头体核的 直接神经纤维投射研究**

**The Research of Direct Nerve Fiber Projections between Ventrolateral Preoptic Nucleus and Tuberomammillary Nucleus in Rats**

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| 指导教师姓名 | 王烈成教授 安徽医科大学基础医学院生理教研室 | | |
| 申请学位级别 | 硕士 | 专 业 名 称 | 病理学与病理生理  学 |
| 提交论文日期 | 2014-3 | 论文答辩日期 | 2014-5-10 |
| 学位授予单位和日期 | | 安徽医科大 | 学 |
|  | | 答辩委员会主席 | |
|  | | 评 阅 人 | |

2014 年 5 月

安 徽 医 科 大 学

**ANHUI MEDICAL UNIVERSITY**

**硕 士 学** 位 论 **文**

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| **论文题目** **大鼠下丘脑腹外侧视前区和结节乳头体核的直**  **接神经纤维投射研究** | |
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| 作者姓名 | 丁 丁 |
| 指导教师 | 王烈成 教授 |
| 学科专业 | Th理学 |
| 研究方向 | 睡眠Th理 |

论文工作时间2012.9 -2014.3

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研究论文

大鼠下丘脑腹外侧视前区和结节乳头体核的直接神经纤维投射研究

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**英文缩略词**

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| **英文缩写** | **英文名** | **中文名** |
| VLPO | Ventrolateral preoptic nucleus | 下丘脑腹外侧视前区 |
| TMN | Tuberomammillary nucleus | 结节乳头体核 |
| GABA | Gamma-amino butyric acid | γ-氨基丁酸 |
| ACSF | Artificial cerebrospinal fluid | 人工脑脊液 |
| NSS | Neurological severityscore | 神经损伤严重程度评分 |
| GAD | Enzyme glutamic acid decarboxylase | 谷氨酸脱梭酶 |
| HDC | Histamine decarboxylase | 组胺脱羧酶 |
| LDT | Dorsolateral brainstem tegmental nucleus | 脑干被盖背外侧核 |
| HA | histamine | 组织胺 |
| LC | Locus coeruleus | 蓝斑核 |
| vPAG | Ventral periaqueductal gray | 腹侧导水管周围灰质 |
| ROC | Receptor-operated calcium channels | 受体操纵钙通道 |
| SNc | Substantia nigra region | 黑质致密区 |
| VTA | Midbrain ventral tegmental area | 中脑腹侧被盖区 |
| DRN | Dorsal raphe nucleus | 背缝神经核 |
| LHA | Rear lateral hypothalamus | 外侧下丘脑后部 |

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| NAC | Nucleus accumbens | 伏隔核 |

中文摘要

**大鼠下丘脑腹外侧视前区和结节乳头体核的直接神经****纤维投射研究**

**目的**

下丘脑腹外侧视前区（ventrolateral preoptic nucleus, VLPO）与结节乳头体核

（tuberomammillary nucleus, TMN）分别是促睡眠中枢和促觉醒调节中枢之一。约80%的VLPO神经元为γ-氨基丁酸（GABA）能神经元和甘丙肽能神经元，而TMN是脑中组胺能神经元胞体集中聚集的区域。本实验采用脑立体定位技术，核团内微量注射、冰冻切片等方法研究VLPO与TMN之间是否具有双向调节的直接通路。

**方法**

1. 模型建立清洁级成年SD大鼠，雌雄不拘，体重250300 g。戊巴比妥钠（50

mg·kg–1）腹腔注射麻醉后，无菌手术操作暴露颅骨，将两个不锈钢引导管（22

gauge）插入VLPO（AP: 0.36 mm; R: 1.30 mm; H: 7.00 mm）和TMN(AP：

3.96 mm；R: 1.50mm；H: 7.70mm）。注射荧光探针后，逐层缝合，送回动物室，自由饮水进食。术后将大鼠置于记录室中休息，待麻醉苏醒后观察动物行为活动。

2. 动物分组将SD大鼠随机分为对照组（TMN+ACSF& VLPO+ACSF组）与实验 组（TMN+ACSF& VLPO+DiO组和TMN+DiO& VLPO+ACSF组）。

3. 药物微量注射使用Hamilton微量注射器（针尖直径26 gauge）通过引导管向目的核团注射ACSF（对照组）或含荧光探针Fast DiO（激发波长488 nm；发射波长，499 nm）（实验组）3l，注射速度为1l·min–1，注射完毕滞针3 min防止药液溢出。

4. 组织学鉴定 大鼠术后72 h后，行戊巴比妥钠（50 mg·kg–1）腹腔注射麻醉并仰卧位固定于手术台上，暴露心脏，从心尖处灌注250 ml生理盐水以及200 ml 4%多聚甲醛。灌注结束后完整取下脑组织并4%多聚甲醛固定24 h，次日使用30%蔗糖PB溶液脱水至沉底。取各组大鼠的大脑的TMN和VLPO进行冰冻切片，片厚2025m，光学显微镜下观察引导管位置以及药物注射位点，仅对定位准确的大鼠进行实验数据的统计。荧光显微下观察Fast DiO标记的荧光效果并拍照。

**结果**

1. 神经损伤严重程度评分（neurological severityscore, NSS）采用双盲法，在ACSF或荧光探针注入核团后2 h和24 h对各组大鼠进行NSS评分。麻醉良好的动物在注射过程中没有发生抽搐、呼吸紊乱等异常情况。术后24 h所有大鼠评分已基本正常。

2. 荧光标记结果

2. 1 TMN+ACSF& VLPO+ACSF组在TMN和VLPO脑区皆未检测到绿色荧光标记神经元。

2. 2 TMN+ACSF& VLPO+DiO组TMN脑区可见明显的绿色荧光标记神经元，荧光均匀存在于细胞质膜中，成像清晰。TMN之外的区域鲜见绿色荧光标记。

2.3 TMN+DiO& VLPO+ACSF组VLPO脑区可见明显的绿色荧光神经元，荧光均匀存在于细胞质膜中，神经元细胞的荧光对比度高，容易辨认，但成像的密度较低。VLPO之外脑区未见荧光。

结 论

VLPO有神经纤维投射至TMN，同时TMN有神经纤维直接投射至VLPO脑区，VLPO

核团与TMN核团存在双向直接联系。

**关键词** 腹外侧视前区；结节乳头体核；大鼠；突触

**Abstract**

**The Research of Direct Nerve Fiber Projections between Ventrolateral Preoptic Nucleus and Tuberomammillary** **Nucleus in Rats**

**Objective**

Ventrolateral preoptic nucleus (VLPO) and tuberomammillary nucleus (TMN) are a sleep-promoting central and a central regulation of arousal, respectively. About 80% of VLPO neurons areγ-aminobutyric acid (GABA) neurons and galanin neurons, while TMN is a concentrated region of histamine neuronal soma in the brain. The brain stereotactic technique, microinjection and frozen section technique are used to investigate the direct nerve fiber projections between VLPO and TMN in rats.

**Methods**

1. Animal model Adult SD rats, male or female, clean grade, weighing about 250-300 g. After sodium pentobarbital (50 mg·kg -1) injected via intraperitoneal injection for anesthesia, the skull was exposed by sterile surgical operations, and the two stainless steel guide tube (22-gauge) were inserted into VLPO (AP: 0.36 mm;

R: 1.30 mm; H: 7.00 mm) and TMN (AP: 3.96 mm; R: 1.50mm; H: 7.70 mm)

In rats. After fluorescent probes injected and skull sutured, the rats were set back to an animal house with free access to water and food. After end all operations, the rats were placed in a recording room to recover from anesthesia and were monitored behavior activities.

2. Grouping SD rats were randomly divided into a control group (TMN+ACSF&

VLPO+ACSF group) and two experimental group (TMN+ACSF&VLPO+DiO group and TMN+DiO&VLPO+ACSF group).

3. Drug microinjection Three microlitres of ACSF (control group) or a fluorescent probe Fast DiO (absorption, 488 nm; emission, 499 nm) (experimental group) were injected by a Hamilton micro syringe (tip diameter 26-gauge) to the destination nucleus with the injecting rate of 1l·min -1, and the injection completed about 3 min to prevent liquid overflow.

4. Histological identification After operated 72 h, line pentobarbital sodium (50 mg·kg -1) was injected via intraperitoneal injection for anesthesia and the rat was fixed on the operating table in the supine position, exposed the heart, and perfused 250 ml of NS and 200ml 4% Paraformaldehyde from the apex cordis. When the perfusion completed, the brain tissue was removed and was fixed by 4%

Paraformaldehyde about 24 h. The the brain tissue was dehydrated and sunk to the bottom in a PB solution containing 30% sucrose on the next day. The frozen brain slices of TMN or VLPO were made with a 20~25μm thickness in each group. The position of the guide tube and drug injection sites were detected under an optical microscope, and the rats which had a correct position were counted. The fluorescent signals labeled by Fast DiO were detected under a fluorescent microscope.

**Results**

1. Modified neurological severity score(mNss) MNss is internationally recognized as the rats after stroke neurological deficit criteria. Highest score 18 points, 1-6 divided into mild damage, 7-12,13-18 minutes of moderate damage and severe damage. After 2 h intraventricular injection markers and 24 h, double-blind, rats in each group mNSS score. The score 1-6 points into experimental groups of rats, abandon the experiment died supplemented rats were randomly.

2. Fluorescently labeled results

2.1 TMN+ACSF&VLPO+ACSF group There are no fluorescence labeled neurons in TMN and VLPO regions.

2.2 TMN+ACSF&VLPO+DiO group There has visible green fluorescence in TMN region and fluorescence uniformly present in the cytoplasm membrance. The fluorescence intensities of neuronal cells are relatively strong with clear image. The regions outside of TMN rare have green fluorescence.

2.3 TMN+DiO&VLPO+ACSF group There has a visible green fluorescence in VLPO region and fluorescence uniformly present in the cytoplasm membrance. The fluorescent contrast of neuronal cells is relatively strong with clear image. But the fluorescent intensity is low. The regions outside of VLPO rare have green fluorescence.

**Conclusion**

VLPO nerve fibers directly project to the TMN, meanwhile TMN nerve fibers directly project to the VLPO areas as well. There have bi-directional nerve fiber projection between VLPO and TMN.

**Keywords**

Ventrolateral preoptic nucleus; Tuberomammillary nucleus; Rat; Synapse

**研究论文**

**大鼠下丘脑腹外侧视前区和结节乳头体核的直接神经纤维投射研究**

# **1.** 前言

在众多生物尤其是人类的生命过程中，都存在明显的时间节律和周期现象，从分子、细胞到机体、群体各个层次，其周期从几秒、几天直至数月、数年。普遍存在的生物节律就是使生物能更好地适应外界环境的时间周期，同时，这种周期性也给生物带来更多的保护。睡眠-觉醒周期是以昼夜为单位的人类和哺乳动物最基本的生物节律之一，正常人的睡醒周期包括了睡眠和觉醒两部分。觉醒和睡眠是大脑的功能状态，在人和动物的觉醒和睡眠期有许多的高级功能活动发生，比如行为、认知和情绪活动等等。

人类生命的1/3时间处于睡眠（sleep）状态，睡眠是健康的三大支柱之一。机体处于睡眠状态时，能瞬间完成睡眠和觉醒的转换。睡眠时有意识活动和运动活动减弱并逐渐消失，新陈代谢下降，机体在能量消耗最小条件下保证机体的基本生命活动，且感知觉与环境分离并丧失部分反应能力的一种可逆转状态，睡眠质量的好坏会影响机体觉醒后各项功能活动的正常进行，左右觉醒时个人才能的发挥程度，同时睡眠障碍则可能会带来降低工作效率、影响生活质量等后果。随着现代生活节奏的加快以及随之带来的生活方式的改变，越来越多的人开始出现睡眠问题。据世界卫生组织2012年的调查结果显示，全球约有29%的人存在不同类型的睡眠问题，其中中国居民睡眠障碍的患病率竟高达42.7%，睡眠问题日益凸显。难以入睡、嗜睡、易醒、多梦、早醒等多种睡眠障碍症状开始不断“骚扰”人们[的生活，好睡眠俨然成为现代都市生活的“奢侈品](http://www.shehuamei.com/)”。各种睡眠障碍性疾患日益成为一个突出的公共卫生和医疗问题而得到人们更多的关注。根据2005年出版的国

际睡眠疾病分类，外在或内在因素导致的睡眠疾病高达90余种，发作性睡病等一

些少见睡眠疾患如今也逐渐被认识和了解。睡眠医学作为一门新兴的边缘交叉学科已经形成并逐渐发展壮大。

研究表明，睡眠和觉醒过程不仅仅是某个神经核团的单独活动，而且是全脑众多神经核团的集体活动（网络活动）过程，睡眠-觉醒周期变化被认为是兴奋性神经元（觉醒产生与维持神经元）与抑制性神经元（睡眠产生与维持神经元）相互之间作用的结果[1, 2]。睡眠-觉醒的发生和维持在结构上需要多个脑功能区和多种神经递质系统的支持。目前研究认为，机体睡眠的产生依赖于下丘脑腹侧和中央视前区的γ-氨基丁酸（GABA）能神经元，觉醒依赖于脑干网状结构的谷氨酸能系统、脑干的胆碱能系统、去甲肾上腺素能系统和基底前脑、5-羟色胺能系统、多巴胺能系统以及下丘脑的组胺能系统和食欲素系统（orexin/hypoeretin）[3]。这些系统在脑内形成了复杂的网络，产生觉醒与产生睡眠的大脑回路相互抑制成为导致觉醒与睡眠两种状态转换的动力。

在十九世纪二十年代的欧洲流行一种脑炎嗜睡病，患者表现为完全缺乏睡眠或者持续性睡眠不能唤醒，同时伴有躁动，直至死亡。意大利神经学家

VonEconomo[4]对病人的尸体进行解剖时发现，下丘脑视前区和基底前脑有严重损伤的病人其临终前临床症状多为睡眠时间减少；而丘脑后部明显损伤的病人临终前临床症状多为嗜睡，由此VonEconomo第一次提出下丘脑靠近视交叉区域含有促睡眠神经元，下丘脑后部含有促觉醒神经元。1946年Nauta在大鼠下丘脑进行毁损实验时也证实了VonEconomo的发现，同时进一步提出了视前区-下丘脑前部为睡眠中枢，下丘脑后部为觉醒中枢，此两个部位的相互作用即为睡眠-觉醒发生转换的驱动力，至此睡眠和觉醒中枢相互抑制的理论得到认可。

随着人们对睡眠问题的重视和深入研究，研究结果表明，下丘脑腹外侧视前区（ventrolateral preoptic nucleus, VLPO）与结节乳头体核（tuberomammillary

nucleus，TMN）分别是促睡眠中枢[5]和促觉醒调节中枢之一[6]。VLPO含有γ-氨基丁酸（GABA）能神经元和甘丙肽能神经元，他们与大脑其他区域有广泛的纤维联系[7]。GABA是哺乳动物神经系统中重要的氨基酸类抑制性神经递质，除存在于

VLPO 及邻近区[8, 9]，还位于下丘脑后部[10, 11]，大脑海马区、小脑、视网膜和脊髓

等部位均存在有GABA能通路[12]，是中枢神经系统的主要抑制性神经元。

1910年，GABA首次在细菌中被发现，然后在昆虫、哺乳类动物体及植物内相继被发现，是非蛋白质组成的一种天然氨基酸，中枢神经系统内的GABA是由谷氨酸脱梭而成的，谷氨酸脱梭酶（GAD）主要存在于脑的灰质中，是GABA合成酶，其大部分以游离的形式存在于神经系统突触末梢的胞质内，参与GABA的合成，少部分以结合形式存在于线粒体内，可使觉醒转化为睡眠[9, 13, 14]。脑中多个部位的GABA神经元共同发挥了促进睡眠的作用。特异性GABA神经元主要包括VLPO含有α有肾上腺素受体的GABA神经元、脑干以及基底前脑和丘脑网状核部位的GABA 神经元，这些神经元根据其兴奋性的不同呈状态选择性的释放

GABA，并发挥抑制激活系统目标神经元的作用。

TMN是脑中组胺能（HA）神经元胞体集中聚集的区域，HA能神经元接受下丘脑外侧区和VLPO的投射纤维，发出广泛的上行和下行纤维大面积投射至几乎所有脑区，下丘脑核团、斜角带及内侧隔核密度最高，其次为基底神经节、大脑皮质及杏仁体，海马、尾核、壳核、嗅球和脑干、小脑、脊髓以及垂体后叶也有少量分布[15, 16]。组氨酸由L-氨基酸转运体转运进入组胺能神经元，通过组胺脱羧酶（HDC）作用生成组胺。单胺转运体将生成的组胺转运入囊泡贮存，囊泡随之释放组胺与其受体结合发挥作用，大部分被突触后膜和神经胶质细胞上的组胺N-甲基转移酶（histamine N-methyltransferase）代谢生成 t-甲基组胺

（t-methylhistamine）从而失去活性[16]。而当N-甲基转移酶活性受到抑制时，组胺则会在二胺氧化酶（diamine oxidase）作用下转化成咪唑乙 醛

（imidazoleacetaldehyde）等物质。

HA能神经元通过纤维投射抑制VLPO睡眠中枢和兴奋大脑皮层，从而发挥促醒的作用；同时视前区GABA能神经元发出纤维投射到下丘脑后部和TMN的HA能神经元[7, 8]，抑制其活动，达到促进睡眠的作用。但是VLPO和TMN之间是否存在直接的双向纤维投射以及其递质释放对睡眠-觉醒节律的形成与维持起何作用是目前研究的热点。

细胞膜荧光探针Fast DiO是一种亲脂性荧光探针，与膜结合或者与亲脂性生

物分子结合时，其荧光强度显著增强。这种荧光探针可以通过细胞膜进入神经末梢，通过逆向轴浆运输到胞体，但是被吞噬后的荧光探针不能从细胞内释放出细胞[20]。因此它是研究中枢核团间是否存在直接投射的理想工具。

为了进一步证实VLPO和TMN核团是否存在双向纤维投射，本实验通过脑立体定位技术，在大鼠的VLPO和TMN脑区分别微量注射荧光探针Fast DiO[20]。该荧光探针是一种可被纤维末梢吞噬，然后经过轴浆运输达到胞体的荧光探针。该类荧光探针进入胞体后不被释放，也就是说仅存在吞噬的神经元内，而不会进入下一级神经元。通过观察TMN和VLPO脑区神经元是否表达有荧光来确定核团间是否有直接投射联系。

# **2.** 材料与方法

## **2.1** 材料

**2.1.1动物**

实验动物采用成年SD大鼠，雌雄不拘，SPF级，体重250-300 g，n = 32，由安徽医科大学实验动物中心提供。所有动物随机分为对照组与实验组。对照组

（TMN+ACSF& VLPO+ACSF组）：VLPO与TMN均微量注射人工脑脊液（ACSF）。实验组：（1）TMN+ACSF& VLPO+DiO组：TMN内微量注射ACSF, VLPO

内微量注射Fast DiO；（2）TMN+DiO& VLPO+ACSF组：TMN内微量注射Fast

DiO, VLPO内微量注射ACSF。

所有实验大鼠均置于室温22-24℃，湿度维持55%以及12 h明/暗（光照08: 00-20: 00）的通风环境中单独饲养，自由饮水与摄食，活动不受限制。实验中SD大鼠的使用严格按照《中华人民共和国实验动物管理条例》和《实验动物质量管理办法》进行。

**2.1.2药品与剂量**

细胞膜荧光探针Fast DiO（Ex=488 nm / Em=499 nm），美国LLC.公司；氯化钠（Sodium Chloride），Sigma

氯化钾（Potassium Chloride），Sigma

磷酸二氢钠（Sodium dihydrogen phosphate），Sigma

氯化镁（Magnesium Chloride），Sigma

氯化钙（Calcium Chloride），Sigma

碳酸亚氢钠（Sodium hydrogen carbonate），Sigma

葡萄糖（Glucos），Sigma

双氧水（Hydrogen peroxide），Sigma

多聚甲醛（paraformaldehyde），Sigma

戊巴比妥钠（Pelltobarbitalum Natricum），中国医药集团上海化学试剂采购供应站分装厂进口分装提供。

**2.1.3仪器**

MP8003型脑立体定位仪深圳市瑞沃德生命科技有限公司

ZH-GSZ高速颅骨钻淮北正华生物仪器设备有限公司

微型计算机联想公司

MODEL 828pH计美国Orion公司

微量注射器瑞士哈美顿博纳图斯股份公司

磁力搅拌器上海梅颖浦仪器仪表制造有限公司

CM1900冰冻切片机德国Leica公司

Heal Force NW超纯水机力康生物医疗科技控股有限公司

DHG-9140A型电热恒温鼓风干燥箱上海精密实验设备有限公司

TG328B型分析天平上海精密科学仪器有限公司天平仪器厂

Nikon 80i免疫荧光正置显微镜日本Nikon公司



## **2.2** 方法.

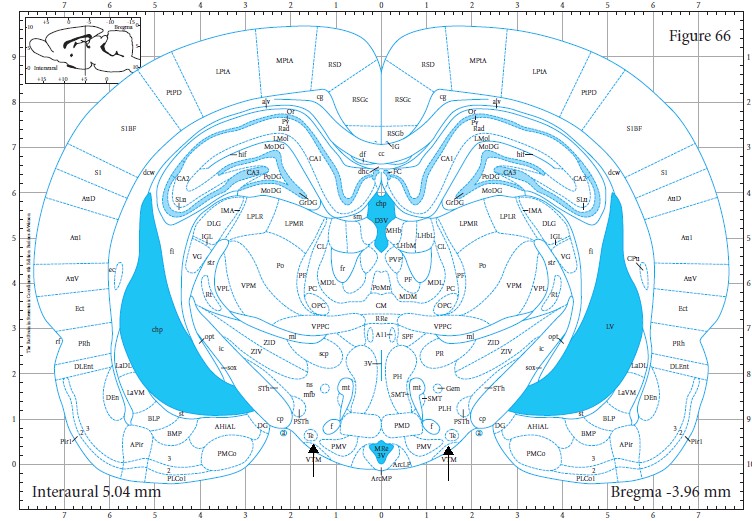
2.1.动物手术

**图1** **主要实验仪器**

**Fig.** **1** **The main experimental apparatus**

经戊巴比妥钠（50 mg/kg）腹腔注射麻醉后，将大鼠头部固定于脑立体定位仪上，常规头部备皮，无菌手术操作暴露颅骨并用0.3%双氧水（H2O2）烧灼清洁颅骨表面，将两个不锈钢引导管（22-gauge）按照Paxinos G and Wstson C大鼠脑立体定位图谱[4]，以前囱为零点，门齿设定在3.3 mm，分别插入VLPO（AP: 0.36 mm; R: 1.30 mm; H: 7.00 mm）和TMN（AP: 3.96 mm; R: 1.50mm; H: 7.70mm），

如图2、3，引导管底端距目的核团2 mm，供VLPO和TMN内微量注射荧光探针使用。



**图2** **埋管示意图（TMN区）**

**Fig.** **2** **Schematic diagram of cannula（TMN）**



**图3** **埋管示意图（VLPO区）**

**Fig.** **3** **Schematic diagram of cannula（VLPO）**

注射完毕后，逐层缝合，大鼠立体定位手术如图4。术后将大鼠置于记录室中休息，自由饮水进食。待麻醉苏醒后观察动物行为活动。



**图4** **大鼠立体定位手术图片**

**Fig.** **4** **A picture of operating rat using stereotaxic apparatus**

**2.2.2药物注射**

使用Hamilton微量注射器（针尖直径26-gauge）通过引导管向目的核团注射。对照组两区域皆注射ACSF(NaCl 147 mol/l, KCl 3 mol/l, CaCl2 1.2 mmol/l, MgCl2

1.0 mmol/l, pH 7.2）3l，注射速度为1l/min；实验组分别向VLPO和TMN注射含荧光探针Fast DiO3l，注射速度为1l/min，注射完毕滞针3~5 min防止药液溢出。

## **2.3** 组织学鉴定

大鼠术后72 h后，腹腔注射戊巴比妥钠（50 mg/kg），麻醉后，仰卧位固定于手术操作台上，暴露心脏，从心尖处进行灌注，首先注入0.01 mmol/L PBS液，待肝脏颜色变淡，心耳处流出液清亮后更换为4%多聚甲醛，先快后慢继续灌注（PBS液用量约200 ml，多聚甲醛用量约250 ml）。灌注结束后完整取下脑组织并4%多聚甲醛固定24 h，次日使用30%蔗糖PB溶液脱水至沉底。取各组大鼠的大脑的

TMN和VLPO进行冰冻切片，片厚20~25m，光学显微镜下观察引导管位置以及药物注射位点，仅对定位准确的大鼠进行实验数据的统计。共计8只大鼠因定位不准确予以剔除实验。荧光显微下观察Fast DiO标记的荧光效果并拍照。

# **3.** 结果

## 3.1 改良神经功能损伤评分（modified neurological severity score，mNSS）是目前国际上公认的大鼠脑卒中后神经功能缺失评判标准。最高分为18分，1-6分为轻度损伤，7-12分为中度损伤，13-18分重度损伤。在标记物注入相应核团后2 h和24 h，采用双盲法，对各组大鼠进行mNSS评分。将评分1-6分的模型大鼠纳入实验分组，摒弃实验中死亡大鼠。

## 3.2 荧光显微镜观察荧光标记效果

3.2.1对照组VLPO与TMN微量注射ACSF后，荧光显微镜下均未检测到带有荧光标记的神经元（图5, 6）。



**图5** **VLPO脑区注射ACSF72h后TMN脑区的显微镜检测**

A：100×镜荧光显微镜检测结果；B: A图的可见光检测结果

**Fig.** **5** TMN **(white line area) photoed under a fluorescence microscope after injected ACSF 72 h in VLPO**

A: A photo taken by a fluorescence microscopy of 100en; B: The same field of figure A taken under

Visible light



**图6** **TMN脑区注射ACSF72h后VLPO脑区的显微镜检测**

A：100×镜荧光显微镜检测结果；B: A图的可见光检测结果

**Fig.** **6** VLPO **(white line area) photoed under a fluorescence microscope after injected ACSF 72h in TMN**

A: A photo taken by a fluorescence microscopy of 100en; B: The same field of figure A taken under visible light

3.2.2 TMN+ACSF& VLPO+DiO组TMN+ACSF& VLPO+DiO组在VLPO核团内注

射荧光探针Fast DiO后72 h, TMN脑区可见明显的绿色荧光，荧光均匀存在于细胞质中，核未清晰显示（图7）。神经元细胞的荧光强度相对强，成像清晰，对比度高，容易辨别。TMN之外的区域鲜见绿色荧光标记，绿色荧光可持续到药物注射后120 h。而VLPO核团内注射ASCF, TMN脑区未见荧光（结果未显示）。



**图7** **VLPO脑区注射Fast DiO72 h后TMN脑区（白线区域）的显微镜检测**

A：100×镜荧光显微镜检测结果；B：200×微荧光显微镜检测结果；C: B图的可见光检测结果

**Fig.** **7** TMN (white line area) photoed under a fluorescence microscope after injected **Fast DiO 72h in VLPO**

A: A photo taken by a fluorescence microscopy of 100en; B: A photo taken by a fluorescence microscopy of 200en; C: The same field of figure B taken under visible light

3.2.3 TMN+DiO& VLPO+ACSF组TMN+DiO& VLPO+ACSF组在TMN核团内注

射荧光探针Fast DiO后72 h, VLPO脑区可见明显的绿色荧光，荧光均匀存在于



细胞质中，核未清晰显示，神经元细胞的荧光对比度高，容易辨认，但成像的密度较低（图8）。而TMN核团内注射ACSF, VLPO脑区未见荧光（结果未显示）。**图8；TMN脑区注射Fast DiO72 h后VLPO脑区（白线区域）的显微镜检测**

A：100×白荧光显微镜检测结果；B：200×微荧光显微镜检测结果；C: B图的可见光检测结果

**Fig.** **8** **VLPO(white line area) photoed under a fluorescence microscope after 72h injected Fast DiO in TMN**

A: A photo taken by a fluorescence microscopy of 100en; B: A photo taken by a fluorescence microscopy of 200en; C: The same field of figure B taken under visible light

# **4.** 讨论

研究表明，睡眠和觉醒过程不仅仅是某个神经核团的单独活动，而且是全脑众多神经核团的集体活动（网络活动）过程，睡眠-觉醒周期变化被认为是兴奋性神经元（觉醒产生与维持神经元）与抑制性神经元（睡眠产生与维持神经元）相互之间作用的结果。Saper等[3]曾提出促睡眠神经元与促觉醒神经元相互抑制的假说，即flip-flop模型，其控制着睡眠觉醒之间的时相转换。VLPO是公认的睡眠调节中枢之一，VLPO中80%的神经元是GABA能和甘丙肽能神经元[8]，并向脑中与觉醒相关的众多区域发出纤维投射[7]，调节睡眠-觉醒时相间的相互转换[7]，被投射的脑区有TMN的组胺能神经元，中缝背核的5-羟色胺能神经元，脑桥被盖核外背侧被盖核的胆碱能神经元以及蓝斑去甲肾上腺素能神经元等等，同时VLPO也接受其它脑区的纤维投射。

谷氨酸是中枢神经系统中重要的兴奋性神经递质，它通过激活NMDA受体，选择性的兴奋相应的神经元胞体，在突触可塑性、突触传递以及神经元溃变过程中发挥重要作用。作为一种抑制性神经递质，GABA 通过GABAA, GABAB 和

GABAC三类受体发挥生理学作用。有研究证实GABA的促眠效应由GABAA受体介导[21-23]. GABAA受体是一种配体门离子通道，其受体复合物的中心部位有一个

GABA门控的Cl通道。当GABA与该受体结合后，会开启细胞膜上的Cl通道，

Cl顺着浓度差由细胞外进入细胞内，使得膜电位增加而发生超极化，产生抑制性突触后电位，发挥抑制细胞兴奋性的效应[24]。

TMN 位于乳头体吻端和视交叉尾侧所形成的下丘脑后部的第三脑室层[25]，

TMN及其邻近区域含有组胺能（HA）神经元，是该神经元在中枢神经系统中聚集的唯一部位，其神经纤维以两条上行和一条下行通路广泛投射至全脑，其中以下丘脑核团，斜角带以及内侧隔核密度最高[15, 16]。是组胺能神经元胞体集中存在的区域[26, 27]，TMN神经纤维除了直接向皮质进行投射，同时还间接地通过丘脑-皮质系统和基底前脑的胆碱能神经元，尤其是位于下丘脑外侧的Orexin能神经元以及基底前脑[28, 29]，共同激活皮质，维持觉醒，并同时接受GABA能抑制性纤维投

射[7,10]。另外，TMN作为睡眠的可控开关在觉醒期间的动作电位发放增强，而在非快动眼睡眠和快动眼睡眠阶段动作电位发放停止[30-32]. Sherin等[8]发现TMN脑区有GABA能神经元末梢，推测此神经末梢来自VLPO。

组胺能神经元中的L-氨基酸转运体（LAT）是表达于细胞膜表面的主要营养物运输系统，为Na＋非依赖的转运系统。组氨酸经LAT转运进入组胺能神经元，经组胺脱羧酶（HDC）作用生成组胺。合成后的组胺被单胺转运体摄取进入囊泡贮存。组胺自囊泡释放后，与其受体结合发挥作用，大部分失去活性，主要被位于突触后膜和神经胶质细胞中的组胺N-甲基转移酶（histamine N-methyltransferase）代谢生成t-甲基组胺（t-methylhistamine）[33]。组胺受体共有4 种亚型，分别为

H1、H2、H3、H4等。其中H1R广泛分布于新皮层、海马、丘脑、下丘脑等脑区，该受体激活后易引起神经元兴奋，细胞信号转导过程与Gq/11蛋白及磷酯酶C耦联[17, 18]；H3R受体位于突触前膜，以自身受体的形式参与负反馈调节组胺的合成与释放；同时H3R 也存在于某些细胞和其他神经元末梢上， 调节γ-氨基丁酸

（GABA）、乙酰胆碱（acetylcholine）、去甲肾上腺素（noradrenalin）等神经递质的释放[19]。

轴浆运输是神经细胞的特性之一。神经元需要不断地从胞体中将各种成分运输至轴突及其分支，也需要从支配的靶组织中摄取营养以维持其正常代谢，有效的轴浆运输必须依赖于完整的神经通路。细胞膜荧光探针一种可通过细胞膜进入纤维末梢，然后经过轴浆运输达到胞体的荧光探针。Fast DiO是一种亲脂性荧光探针，与膜结合或者与亲脂性生物分子结合时，其荧光强度显著增强。这种荧光探针可以被神经末梢吞噬，通过逆向轴浆运输到胞体，但是被吞噬后的荧光探针不能从细胞内释放出细胞[20]。因此是研究中枢核团间是否存在直接投射的理想工具。

我们另一部分研究结果显示VLPO神经元可通过抑制TMN神经元的活动产生促睡眠效应[35]。本实验主要研究了探讨促睡眠调节中枢下丘脑腹外侧视前区与促觉醒调节中枢结节乳头体核之间的神经纤维投射关系。本实验中，我们应用了自由活动装置，更好的模拟了其生理状态下的睡眠-觉醒周期。关于VLPO与TMN之间的神经调节机制有待进一步阐明。

# 5. 结论

本研究提示：

VLPO发出的神经纤维可直接投射至TMN，并且TMN发出的神经纤维也可直接投射至VLPO脑区，故VLPO核团与TMN核团间存在双向直接纤维投射。

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附**录**

**本人简历：**

丁丁，女，1981年5月出生，籍贯：安徽省五河县。

1996年9月—1999年7月，就读于安徽省五河县第一中学；

1999年9月—2004年7月，就读于安徽医科大学临床医学系，本科学历；

2004年7月至今，安徽医学高等专科学校，学生处工作；

2007年9月至今，攻读安徽医科大学同等学历硕士。

**攻读硕士学位期间参加的科研课题：**

国家自然科学基金资助项目（81071075）；

教育部博士点基金新教师类（20093420120004）；

安徽医科大学校科研基金（2013xkj002, 2013xkj005）

**攻读硕士学位期间发表的文章：**

1.吴芳，张瑾，丁睿，江传玮，解敏，许奇，丁丁，王烈成.下丘脑腹外侧视前区通过抑制结节乳头体核对大鼠睡眠觉醒进行调控. 2014，中华行为医学与脑科学杂志，2014,23(2)：97-100.

**2.** 丁丁，丁睿，吴芳，张瑾，许奇，解敏，王烈成. 大鼠下丘脑腹外侧视前区和结节乳头体核的直接神经纤维投射研究.2014.安徽医科大学学报. 已接收，待刊出。

致 **谢**

值此学位论文完成之际，我谨向所有关心、爱护、帮助过我的人表示最诚挚的感谢与最美好的祝愿！

本论文是在导师王烈成教授的悉心指导之下完成的。两年来，王教授渊博的

专业知识，严谨的治学态度，精益求精的工作作风，诲人不倦的高尚师德，朴实无华、平易近人的人格魅力对我影响深远。作为一名在职研究生，王教授不仅授我以文，而且教我做人，从他的身上我深深体会为人师表的意义，这些将赋予我终生受益无穷之道，在此，我再次郑重的向王烈成教授表达深深的谢意和感激之情。

本论文从选题到完成，几易其稿，每一步都是在王教授的指导下完成的，倾注了导师大量的心血！本论文的完成也离不开其他各位老师、同学和朋友的关心与帮助。在此也要感谢在论文开题、初稿、预答辩期间各位教授所提出的宝贵意见，还要感谢同门师弟师妹吴芳、丁睿等人，在科研过程中给我以许多启发、鼓励和帮助。回想整个论文的写作过程，虽有不易，却让我除却浮躁，经历了思考和启示，也更加深切地体会了科学的精髓和意义，因此倍感珍惜。

**综述**

**睡眠-觉醒节律的神经调节机制**

**摘要：**睡眠觉醒有着复杂的神经调节机制，是涉及多系统、多中枢的生理过程。研究证实促进大脑觉醒的系统绝大部分起源于一系列明确的细胞群，并且与各自明确的神经递质相关联。促进睡眠的系统主要与中抑制性神经递质氨基丁酸(GABA)有关，脑中不同部位的GABA神经元共同协作起到促进睡眠的作用。为了更好的了解睡眠觉醒的神经调节机制，本文对促进觉醒的系统和促进睡眠的系统的功能及其有关的神经递质展开综述。

**关键词**：睡眠； 觉醒； 神经递质

The neural regulatory mechanisms of sleep-wake cycle

**Abstract:** There have complex neural mechanisms in sleep-wake cycle, which are involved in multi-system, multi-hub physiological processes. The studies have confirmed that most of the originated nucleus and its specific neurotransmitters of promoting arousal system in brain are been confirmed. The promoting sleep system is mainly associated with inhibitory neurotransmitter, gamma-aminobutyric acid (GABA). Those different parts of GABA neurons work together to play a role in promoting sleep. In order to better understand the neural mechanisms regulating the sleep-wake cycle, this article summarizes the progress of the promoting arousal system and promoting sleep system and their related neurotransmitters.

**Key words:** sleep;; wake;; Neurotransmitter

**1. 前言**

睡眠觉醒是人类的基本生理行为。在觉醒期，除了行为活动之外，还具有活跃的脑电波，即高频率低电位皮质脑电。睡眠期分为两个基本阶段：慢波睡眠和快动眼睡眠，前者出现在睡眠初始阶段，伴随低频率高电位脑电；后者出现在睡眠开始后90分钟左右，此期脑电兴奋性明显增高[1] 。

睡眠觉醒的发生和维持在结构上需要多个脑功能区和多种神经递质系统的支

持。目前认为睡眠依赖于腹侧和中央视前区的γ-氨基丁酸（GABA）能神经元，觉醒依赖于脑干网状结构的谷氨酸能系统、基底前脑和脑干的胆碱能系统、脑干的去甲肾上腺素能系统、5-羟色胺能系统和多巴胺能系统以及下丘脑的组胺能系统和食欲素系统（orexin/hypoeretin）[2]。这些系统在脑内形成了复杂的网络，产生觉

醒与产生睡眠的大脑回路相互抑制，导致觉醒与睡眠两种状态的转换，且这种转换具有瞬时性。在这两种状态的转换过程中，外侧下丘脑的食欲素能神经元起到稳定性作用[3]。脑干网状结构的谷氨酸能系统在觉醒和REM睡眠中放电明显增加

[4,5]。

**2. 促进觉醒的系统**

研究表明，促进觉醒的系统大部分来源于一系列明确的细胞群，并且与各自明确的神经递质相关联[6]。促进觉醒的系统有两条主要的激活路径[3]，一是由脑干被盖背外侧核（LDT）和脑桥被盖网状核（PPT）通过乙酰胆碱激活丘脑中继核和网状核，从而将信号传递到大脑皮质；二是由来自不同神经核团的信号先激活外侧下丘脑和基底前脑后再激活大脑皮质。这些神经核团主要包括：结节乳头体核

（TMN）组织胺能神经元、腹侧导水管周围灰质（vPAG）多巴胺能神经元、背侧和正中脊核5-羟色胺能神经元和蓝斑核（LC）去甲肾上腺素能神经元，多起源于上位脑干和尾侧下丘脑部位的单胺能神经元。而第二条激活途径也同时接受来自外侧下丘脑食欲素能神经元、基底前脑GABA和乙酰胆碱能神经元所传导的信号。下

面对激活系统中主要的神经递质进行表述。

2.1食欲素

1998年Sutcliffe[7]的研究小组在下丘脑中新发现了一种含有130个氨基酸的神经肽，即食欲素（Orexin）。食欲素分为A、B两个亚型，中枢食欲素能神经元胞体对称分布在侧下区及穹窿周围区，其发出的神经纤维能投射到包括皮质、海马、伏核、下丘脑、丘脑、腹侧背盖区等的广泛区域。后来也在外周器官组织如肾上腺及胰腺、消化道等外周器官检测到相当数量的食欲素，最初的研究也因此集中在摄食能量代谢相关的领域。随着研究的深入，发现食欲素具有强烈的促醒作用，研究方向也转移到了睡眠-觉醒的调节方面[8]。已有研究表明食欲素的缺失可以改变觉醒睡眠周期[9]，在狗、大鼠、人类中都已得到了充分的证实。相反，在食欲素

治疗患有嗜睡症的个体中，在某些核团或脑功能区，如松果体、垂体，食欲素能细胞具有神经元及内分泌的双重功能，这些神经元多由下丘脑相关神经元投射。食欲素A在生理状态下具有比食欲素B更高的稳定性，食欲素A也具有更强的脂溶性，更容易穿过血脑屏障及细胞膜，这可能是在脑脊液中检测到较多食欲素A的原因[10]。目前的研究表明，食欲素主要通过受体操纵钙通道（ROC）及钙池调控钙通道（SOC）升高细胞内钙离子浓度来提高细胞兴奋性[11]。在ROC途径中食欲素通过激活PLC、PKC，引起L型钙通道开放，胞内钙增加，食欲素受体在与食欲素结合后与G蛋白偶联[12]，激活PLC，产生IP3和甘油二酯等第二信使物质[13]，使胞浆中Ca2+

浓度升高。而SOC途径是一种由胞内内质网释放钙离子触发的细胞膜上钙离子通道

开放的过程，尽管已发现20余年，但其机制依然处于假说阶段。除此之外，当细胞处于无钙环境中时并不会触发SOC途径[14]。以往的实验也表明食欲素对突触前和突触后神经元均有明显作用[15]。研究表明，觉醒期食欲素神经元主要为兴奋状态，尤其在动物主动探究行为过程中兴奋性更高[16]。食欲素神经元上行投射到大脑皮质，下行投射到所有与激活系统相关的单胺能和胆碱能细胞[17]。腹外侧视前区神经元和食欲素神经元之间相互都有纤维投射，但前者区域内没有食欲素受体。因此，食欲素神经元增强了上行激活系统的功能，但它并不直接抑制腹外侧视前区。这种不对称的投射关系能够有助于睡眠觉醒转换的稳定，避免了不必要的觉醒睡眠状态的转换。患有发作性睡眠病的人和动物缺乏这种影响，他们的总睡眠时间并不比普通个体多，但在白天他们容易嗜睡，而在夜间睡眠时又容易醒来[18]。

2.2乙酰胆碱

位于LDT和PPT的胆碱能神经元在觉醒期及快动眼睡眠期兴奋性最高，在慢波睡眠期则兴奋性降低，与大脑皮质的兴奋性活动相吻合[19]。这些胆碱能神经元通过释放乙酰胆碱激活丘脑中继核和网状核。因网状核位于丘脑中继核与大脑皮质之间，起到丘脑和大脑皮质之间信息传递的门控作用，对网状核的信号输入至关重要。

2.3 5-羟色胺

人体有1%-2%的5-羟色胺分布在中枢神经系统的中缝核群，中缝核群的5-羟色胺能神经元占总数的77.5%，其纤维主要投射到前脑，其余的大部分散布在脑干其

他区域。多年前人们就意识到5-羟色胺的调节睡眠作用，但对其作用机制及作用部位一直存在较大争议。近年来的微透析实验表明，在觉醒期大多数具有5-羟色胺能神经元纤维投射的皮质及皮质下区域的5-羟色胺水平明显升高，与中缝背核5-羟色胺能神经元的兴奋性一致。在觉醒期间，中缝背核区域表现出最高兴奋性，接着

在慢波睡眠期兴奋性降低，而在快动眼睡眠期兴奋性最低。说明在觉醒期5-羟色胺有促进觉醒的作用，参与了抑制快动眼睡眠[20]。Chastrette等[21]认为5-羟色胺具有缓慢促进位于下丘脑的具有催眠效应的肽类物质聚集的作用，而5-羟色胺的耗竭则使机体失去这些催眠物质的作用。这也同时解释了睡眠剥夺后出现的睡眠反弹现

象，在睡眠剥夺期持续高水平的5-羟色胺转换率进行性的增加下丘脑多肽的聚积，导致睡眠反弹。

2.4多巴胺

中枢神经系统的多巴胺神经元集中在黑质致密区（SNc）和中脑腹侧被盖区

（VTA），末梢分别投射到背缝神经核（DRN）、PPT、LDT、LC、外侧下丘脑后部

（LHA）、基底前脑和丘脑。在睡眠觉醒周期的转换中，SNc和VTA部位的多巴胺神经元在睡眠觉醒周期的平均放电频率没有变化，中脑部位多巴胺神经元变化的是放电模式而不是放电频率。在觉醒期，多巴胺神经元脉冲式放电活动增多，VTA、

伏隔核（NAC）和前脑一些部位的多巴胺释放增加[22]。Lin等[23]在对觉醒期多巴胺中枢神经作用部位的研究中发现一些拟多巴胺药物通过对前脑基底部及脑干区域的作用促进觉醒延长，不同于如穿梭运动等定型活动通过对纹状体的作用从而发挥相应效应。

2.5去甲肾上腺素

大脑去甲肾上腺素能神经元胞体分布相对集中，主要分布在脑桥和延髓，但去甲肾上腺素神经元胞体密集在LC，LC上行发出三束投射纤维，分别为中央被盖束、中央灰质背纵束和腹侧被盖内侧前脑束，这3束纤维主要同侧上行支配大脑皮质各区及边缘系统，LC下行纤维投射到延髓及脑桥。去甲肾上腺素是重要的促进觉醒的神经递质，具有遗传性多巴胺到去甲肾上腺素转化缺陷的小鼠的去甲肾上腺素能受体激活作用减弱，导致睡眠时间延长并在应激状态下不易被唤醒。去甲肾上腺素受体有大量的亚型，因此无法清楚其受体的激活或拮抗作用与觉醒的关系。

然而，有研究者认为突触部位去甲肾上腺素水平的改变会对觉醒产生影响[24]。

Hobson等[25]提出在快动眼睡眠LC去甲肾上腺素能神经元兴奋性降低，单胺能神经元对快动眼睡眠期起到抑制作用。Aston-Jones和Bloom通过在猫体内实验也发现了

LC神经元兴奋性降低的现象，并被Jacob等所证实。还有研究表明LC兴奋性降低可以诱导慢波睡眠和快动眼睡眠，轻微兴奋LC可以缩短快动眼睡眠，因此，LC也被称为快动眼睡眠关闭结构。

2.6组胺

结节乳头体核组胺细胞群发出神经纤维投射到前脑和脑干，这些细胞在觉醒期兴奋性升高，在睡眠期间则受到位于下丘脑的GABA神经元的抑制。结节乳头体核部位的神经元损伤或者阻断组胺受体尤其是组胺H1受体，能够导致嗜睡。因此，抗组胺类药物常有导致嗜睡的副作用[26]。

**3. 促进睡眠的系统**

GABA是主要的抑制性神经递质，脑中不同部位的GABA神经元共同起到了促进睡眠的作用。特异性GABA神经元主要包括基底前脑和VLPO含有α2肾上腺素受体的

GABA神经元以及脑干和丘脑网状核部位的GABA神经元，其根据兴奋性的不同呈状态选择性的释放GABA，并起到抑制激活系统目标神经元的作用。因此，普通的催眠和麻醉药物能增强GABA介导的神经传递[27]。下面对不同大脑功能区域促进睡眠的GABA神经元进行介绍。

2.1 脑干的谷氨酸能神经元

位于脑干的网状结构上行激活系统对生物觉醒有着重要的作用。早在1949年，

Molllzzi等通过动物实验观察到毁损中脑网状结构后导致昏迷，电刺激网状结构引起皮层脑电的去同步化并伴随着觉醒的发生。这些实验明确了位于脑桥喙部和中脑尾部连接处的脑区对维持觉醒起着关键作用这一机制[28]。位于脑桥喙部旁臂核和毗邻蓝斑前区的谷氨酸能神经元是上行觉醒激活系统的主要来源之一。目前研

究发现这些神经元可以投射到下丘脑影响前脑的功能活动，还可以投射到丘脑经丘脑中继而影响大脑皮层的活动[29-31]。电生理记录和c-Fos研究都显示这些神经元是觉醒活动的神经元，参与觉醒活动的调节[30, 32, 33]。来自脑桥和延髓背侧的神经元，推测是谷氨酸能神经元，其投射到前脑和脊髓，易化皮层活动或者发出易化性网

状脊髓束达脊髓前角细胞，从而调节脊髓牵强反射以及肌张力[34, 35]。但是这些研究未能分析核团内功能的异质性，即使是同一个核团的不同分区其作用也可能不同。研究证明，脑桥喙部旁臂核旁侧部分参与二氧化碳诱发的觉醒，而脑桥喙部旁臂核中间部分则在促进自发觉醒中起着重要的作用[36]。

脑干在REM睡眠的发生中同样起着关键的作用。目前认为脑干存在促REM睡眠的神经元和抑制REM睡眠的神经元[30]。实验表明，脑桥的下外侧背核和蓝斑前区以及外背侧被盖核和桥脚被盖核的神经元在REM睡眠时c-Fos表达增加，属于REM-on神经元[30,37]。通过逆行追踪技术，确定了外背侧被盖核主要的抑制性GABA能神经传人纤维来自中脑导水管灰质的腹侧和毗邻的侧脑桥被盖[30,38]区域，所以这两个脑区的神经元可以抑制REM睡眠，属于REM-off神经元。这些发现证实REM-on和REM-off以一种相互抑制的关系实现对REM睡眠开关的控制，并被形容为跷跷板

开关(flip-flop switch)[6]。最近有人认为是外背侧被盖核的REM—on谷氨酸能神经元而不是GABA能神经元控制REM-off从而引起REM睡眠发生[39]。

脑干的谷氨酸能神经元混在REM-onGABA能神经元中间，发出长投射激活控制

REM睡眠的主要结构[30]。外背侧被盖核谷氨酸能神经元在REM睡眠时，会有c-Fos蛋白表达，其向脑干和脊髓抑制系统发出的投射可以激活一系列延髓和脊髓中的抑制性中间神经元，最终引起运动神经元的超极化和肌无力[30,40]。另外，在REM-off

GABA能神经元中间也混杂着一些REM-off谷氨酸能神经元，并投射至脊髓来维持慢波睡眠时的肌张力[41]。位于脑桥喙部旁臂核和毗邻蓝斑前区的谷氨酸能神经元可投射至前脑并调节REM睡眠时相的脑电成份[30]。

2．2 外侧下丘脑的谷氨酸能神经元

外侧下丘脑是位于前脑的重要的觉醒核团之一，目前研究比较多的是其中的食欲素神经元。食欲素是由外侧下丘脑区域特异的一组神经元合成分泌的一种神经多肽[42]。食欲素神经元广泛地投射到皮层至脊髓的整个中枢神经系统，参与摄食、觉醒和动机性行为[43]。食欲素神经元单独兴奋就足以引起动物脑电的去同步化和行为上的觉醒[44]。有很多的食欲素神经元同样释放谷氨酸[45]，食欲素和谷氨酸可共同定位在同一个突触末梢但不同的囊泡内，从而实现两者的共同释放。由于食欲素的释放比谷氨酸的释放需要更高的动作电位频率[46]，所以食欲素神经元

低频动作电位发放时主要以释放谷氨酸为主，更高的动作电位频率才能促使额外的食欲素释放加快觉醒。

外侧下丘脑的很多神经元都能表达Ⅱ型谷氨酸转运体[47]，说明它们存在谷氨酸能突触末梢通过局部释放谷氨酸进而调节食欲素神经元活动。Yamanaka等[48]证明谷氨酸通过谷氨酸受体使外侧下丘脑的食欲素神经元去极化，也有报道证实食欲素通过局部谷氨酸能神经元增加谷氨酸释放激活食欲素神经元，参与下丘脑的唤醒系统[49]。这些谷氨酸能投射可能来自基底前脑，因为在结构上存在基底前脑的谷氨酸能纤维投射至外侧下丘脑的食欲素神经元，从而维持行为觉醒及肌张力

[50]. 另外，外侧下丘脑的食欲素神经元到基底前脑神经元的投射被认为是食欲素

神经元促觉醒的关键结构[51]。因此外侧下丘脑与基底前脑存在相互的兴奋性作用，对于提高动物在特殊情况下的警觉有着重要的生理意义。但对外侧下丘脑局部是否存在谷氨酸能神经元并释放谷氨酸从而影响觉醒目前尚缺乏研究报道，之前的研究多在离体水平阐述外侧下丘脑中谷氨酸的作用，在体水平研究外侧下丘脑的谷氨酸释放对觉醒的影响尚未成熟。

2.3基底前脑的谷氨酸能神经元

基底前脑在皮层活动、睡眠、记忆中起重要的作用，也是皮层下最重要的觉醒激活系统[2]。该区域中有胆碱能神经元、GABA能神经元、谷氨酸能神经元，及其它未被识别的神经元[52]，这些神经元通过末梢释放乙酰胆碱、GABA和谷氨酸来影响皮层和皮层下结构的活动[53]。虽然在基底前脑内只有约5％的神经元有能力合成乙酰胆碱[53]，但这些胆碱能神经元可广泛投射到皮层[54]，在觉醒和REM睡眠的皮层活动中起重要作用[55]。

目前对基底前脑谷氨酸的研究不多，研究表明在基底前脑内存在大量（85％～

90％）能够合成谷氨酸的神经元[53]，且这些谷氨酸能神经元是可兴奋的；在结构上也存在基底前脑的谷氨酸能神经末梢与胆碱能神经元形成的突触[56]，均提示基底前脑的谷氨酸能神经元可作为兴奋性中间神经元起兴奋胆碱能神经元的作用，即谷氨酸能神经元对皮层的促觉醒作用可能是通过胆碱能神经元发挥作用的。细胞在体电生理记录结合免疫组化证实在基底前脑存在与睡眠觉醒时相相关的谷氨酸能神经元，且它们的放电与肌电活动呈正相关[57]。

在基底前脑内也有谷氨酸受体的表达[58]，应用谷氨酸能受体的激动剂能够使神经元c-fos表达增加，皮层的乙酰胆碱释放，脑电去同步化同时抑制睡眠[59]。基底前脑的这些谷氨酸可能来自基底前脑神经元的末梢释放[60]，也可能来自食欲素神经元或者来自皮层、丘脑和桥脚被盖核[61]。由于目前电生理、药理学、形态学的结果尚不能对基底前脑内的谷氨酸的作用及来源给出肯定的答案，可以借助光遗传学的手段特异地操控基底前脑的谷氨酸释放来研究该脑区谷氨酸的作用。在

基底前脑除了存在谷氨酸能神经元投射至胆碱能神经元引起皮层觉醒外，还存在由基底前脑直接投射到内嗅皮层或前额叶皮层的谷氨酸能神经元[52]，这两种投射方式可能均参与基底前脑谷氨酸能神经元对皮层的促觉醒作用。

基底前脑除与皮层的突触联系外，另一个联系密切的结构是外侧下丘脑，外侧下丘脑与基底前脑存在相互兴奋作用，25％的在基底前脑投射到外侧下丘脑的神经元是谷氨酸能神经元[50]，这部分谷氨酸能神经元直接作用外侧下丘脑的食欲素神经元，从而广泛的投射到所有靶点，同时促进皮层激活和行为唤醒。这种兴奋性可能与基底前脑的谷氨酸能神经元在清醒时能最大限度的活跃，又在慢波和

REM睡眠时能最低限度的活跃有关，基底前脑内的GABA能神经元也会投射到外侧下丘脑，所以基底前脑神经元对外侧下丘脑有双重的作用，既兴奋又可以抑制外侧下丘脑的神经元活动。

2.4大脑皮层的谷氨酸能神经元

大脑皮层不仅是觉醒系统的最终作用靶点，它本身也参与觉醒调节。皮层下激活系统的各部分向上投射并支配前额叶皮层，尤其是中间前额叶皮层。反之，中间前额叶皮层也能下行投射回到基底前脑、下丘脑、脑干等觉醒激活系统的各部分脑区[62]。大脑皮层神经元主要接受基底前脑和丘脑的神经传入。研究证实，

基底前脑的胆碱能神经元、GABA能神经元和谷氨酸能神经元都能投射到前额叶皮层的谷氨酸能神经元和中间神经元，以弥散方式影响皮层觉醒[63]，而皮层的轴突也可以通过支配基底前脑的抑制性和非胆碱能神经元，对基底前脑神经元的活动进行调节[62]，可能是前额叶皮层调节觉醒的一个机制。大脑皮层作的结构与功能的分区可以更好的研究谷氨酸的作用。由于缺乏广泛兴奋皮层谷氨酸的有效手段，而觉醒的维持还需要皮层广泛的兴奋，目前对皮层研究谷氨酸对觉醒过程的作用

与机制缺乏全面的认识。

丘脑是大脑皮层下谷氨酸投射至皮层最重要也是最丰富的来源，丘脑层内核和中间核的谷氨酸能神经元也弥散地投射到皮层[64]，但这些纤维投射在觉醒中能否起主要作用尚不明确。而皮层和皮层下结构的相互兴奋会使动物中间前额叶皮层在存在刺激的情况下快速的觉醒。

综上，脑干的谷氨酸既参与清醒时脑活动调节和肌张力的维持，同时又调节

REM睡眠时相的脑电的构成和肌无力；外侧下丘脑的谷氨酸通过激活食欲素神经元参与下丘脑的唤醒系统；基底前脑的谷氨酸参与脑电去同步化及睡眠抑制；皮层的谷氨酸则是觉醒系统的最终作用靶点。

4．展望

除上述调节因素外，昼夜节律、内稳态过程等也参与了睡眠觉醒的调节。

Zoltowski等[65]研究一种真菌的生物钟，其通过一种感光蛋白和一系列细胞内过程，将光能转化成化学反应的生理机制，发现生物钟使真菌在需要防护的时候才合成类胡萝b素。而类似的“开关”机制可能也存在于人类的睡眠机制中。目前对于睡眠觉醒的整体调节机制尚未完全清楚，因此，理清各个影响因素之间的相互作用和影响，从整体阐述睡眠觉醒的机制成为学者关注的重点。

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