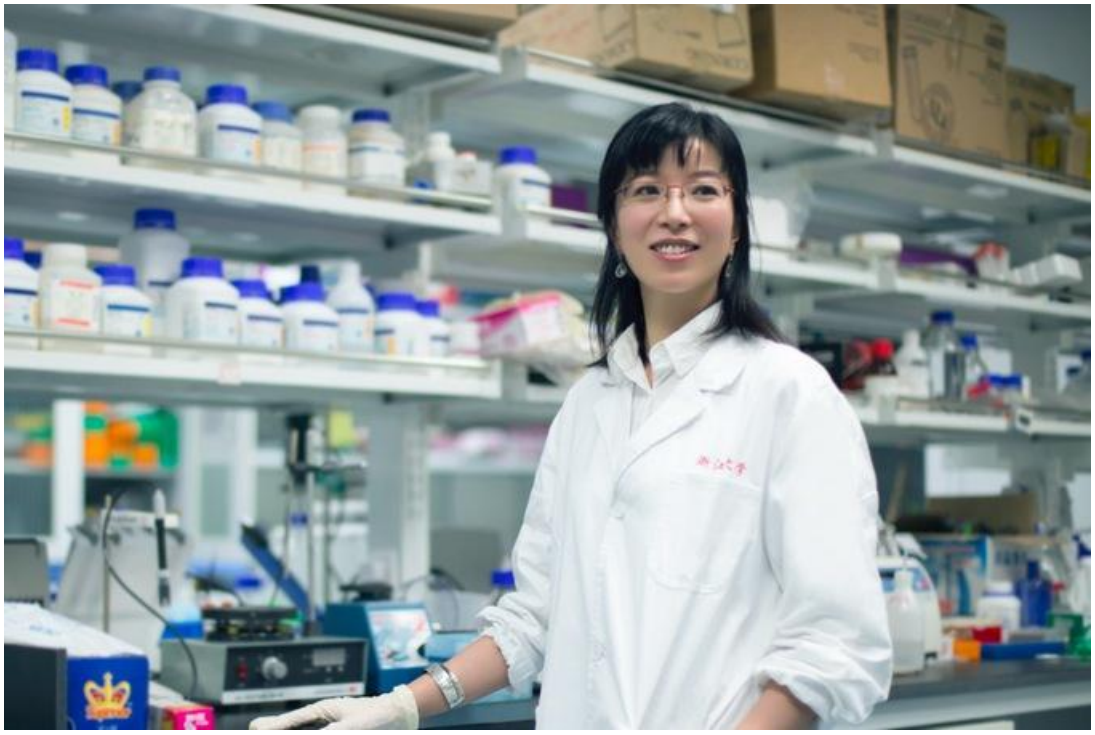
同期 2 篇 Nature！浙大胡海岚团队：突破世界性难题

The group of Hailan Hu Resolved a World-class Puzzle for Depression by Two Research Articles



2 月 14 日，浙江大学医学院和求是高等研究院胡海岚团队在《Nature》期刊同时发表两篇研究长文，揭示了团队在抑郁症研究方面取得的重大突破。他们发现快速抗抑郁分子的作用机制，推进人类关于抑郁症发病机理的认知，并为开发新型抗抑郁药物提供多个崭新的分子靶点。

作为影响人类生活最严重的精神疾病之一，抑郁症越来越受到关注。多年研究表明，抑郁症并不是简单的心理出现问题，而是大脑发生了病理性的改变。遗憾的是，目前的抗抑郁药物起效慢、有效率低。这意味着我们对抑郁症机制的了解可能还没有触及核心。

在题为“Ketamine blocks bursting in the lateral habenula to rapidly relieve depression”的文章中，胡海岚团队首次揭示了外侧缰核的一种特殊放电方式——簇状放电是抑郁症发生的充分条件，而氯胺酮的起效原因正是有效阻止了这一脑区的簇状放电。“这一系列研究阐明了氯胺酮快速抗抑郁的全新脑机制——即氯胺酮可以通过阻断外侧缰核的簇状放电，进而释放对下游单胺类奖赏脑区的过度抑制，最终产生快速抗抑郁的疗效。”胡海岚说。

在同时发表的另一篇“Astroglial Kir4.1 in lateral habenula drives neuronal bursts in depression”文章中，胡海岚团队揭示了另外一个快速抗抑郁分子靶点——存在于胶质细胞中的的钾离子通道 Kir4.1，对引发神经元的簇状放电至关重要。在这一系列研究中，

胡海岚团队陆续指出了谷氨酸受体 NMDAR、T-VSCCs、Kir4.1 作为快速抗抑郁分子靶点的有效性。她认为：“虽然药物研发的道路很漫长，但是我们已经看见了曙光，并且迈出了第一步。”

Ketamine blocks bursting in the lateral habenula to rapidly relieve depression

氯胺酮通过抑制大脑外侧缰核的一种特殊放电方式,快速缓解抑郁症

浙江大学 胡海岚

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The N-methyl-D-aspartate receptor (NMDAR) antagonist ketamine has attracted enormous interest in mental health research owing to its rapid antidepressant actions, but its mechanism of action has remained elusive. Here we show that blockade of NMDAR-dependent bursting activity in the ‘anti-reward center’, the lateral habenula (LHb), mediates the rapid antidepressant actions of ketamine in rat and mouse models of depression. LHb neurons show a significant increase in burst activity and theta-band synchronization in depressive-like animals, which is reversed by ketamine. Burst-evoking photostimulation of LHb drives behavioural despair and anhedonia. Pharmacology and modelling experiments reveal that LHb bursting requires both NMDARs and low-voltage-sensitive T-type calcium channels (T-VSCCs). Furthermore, local blockade of NMDAR or T-VSCCs in the LHb is sufficient to induce rapid antidepressant effects. Our results suggest a simple model whereby ketamine quickly elevates mood by blocking NMDAR-dependent bursting activity of LHb neurons to disinhibit downstream monoaminergic reward centres, and provide a framework for developing new rapid-acting antidepressants.

Astroglial Kir4.1 in the lateral habenula drives neuronal bursts in depression

钾离子通道 Kir4.1 促进外侧缰核的簇状放电

浙江大学 胡海岚

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Enhanced bursting activity of neurons in the lateral habenula (LHb) is essential in driving depression-like behaviours, but the cause of this increase has been unknown. Here, using a high-throughput quantitative proteomic screen, we show that an astroglial potassium channel (Kir4.1) is upregulated in the LHb in rat models of depression. Kir4.1 in the LHb shows a distinct pattern of expression on astrocytic membrane processes that wrap tightly around the neuronal soma. Electrophysiology and modelling data show that the level of Kir4.1 on astrocytes tightly regulates the degree of membrane hyperpolarization and the amount of bursting activity of LHb neurons. Astrocyte-specific gain and loss of Kir4.1 in the LHb bidirectionally regulates neuronal bursting and depression-like symptoms. Together, these results show that a glia–neuron interaction at the perisomatic space of LHb is involved in setting the neuronal firing mode in models of a major psychiatric disease. Kir4.1 in the LHb might have potential as a target for treating clinical depression.