

## Anticonvulsant effects of leptin in epilepsy

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### Commentary

Secreted from adipose tissue at levels proportional to fat stores, the hormone leptin is a critical regulator of the hypothalamic machinery that controls feeding and energy metabolism. Despite the critical role of leptin in the maintenance of energy homeostasis, no leptin-based therapeutic approaches have emerged to combat metabolic disorders such as obesity or diabetes. In this issue of the *JCI*, Xu et al. report a robust influence of leptin, beyond its role in metabolism, on hippocampal neuronal processes implicated in the etiology of epileptic seizures, learning, and memory (see the related article beginning on page 272). They show, in two rodent seizure models, that leptin administered directly to the brain or nasal epithelium suppresses seizures via direct effects on glutamate neurotransmission in the hippocampus. These observations suggest that leptin may have therapeutic potential in the treatment of epilepsy and strengthen the notion that peripheral metabolic hormones such as leptin play important roles in the regulation of higher brain functions.

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conserved in mature animals and human disease states, clear demonstration of the validity of such predictions is often lacking and requires complex genetic and physiologic approaches. The studies in this issue of the *JCI* identify AM signaling as a key regulator of blood and lymphatic vessel function, but whether Starling would be disappointed or gratified to learn of the persistent significance of his experiments in our molecular and genetic age is not clear. Clear definition of the vascular roles of AM signaling will parallel progress in addressing these broad issues in vascular biology, leaving plenty of future work for these and other investigators.

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## Anticonvulsant effects of leptin in epilepsy

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**Secreted from adipose tissue at levels proportional to fat stores, the hormone leptin is a critical regulator of the hypothalamic machinery that controls feeding and energy metabolism. Despite the critical role of leptin in the maintenance of energy homeostasis, no leptin-based therapeutic approaches have emerged to combat metabolic disorders such as obesity or diabetes. In this issue of the *JCI*, Xu et al. report a robust influence of leptin, beyond its role in metabolism, on hippocampal neuronal processes implicated in the etiology of epileptic seizures, learning, and memory (see the related article beginning on page 272). They show, in two rodent seizure models, that leptin administered directly to the brain or nasal epithelium suppresses seizures via direct effects on glutamate neurotransmission in the hippocampus. These observations suggest that leptin may have therapeutic potential in the treatment of epilepsy and strengthen the notion that peripheral metabolic hormones such as leptin play important roles in the regulation of higher brain functions.**

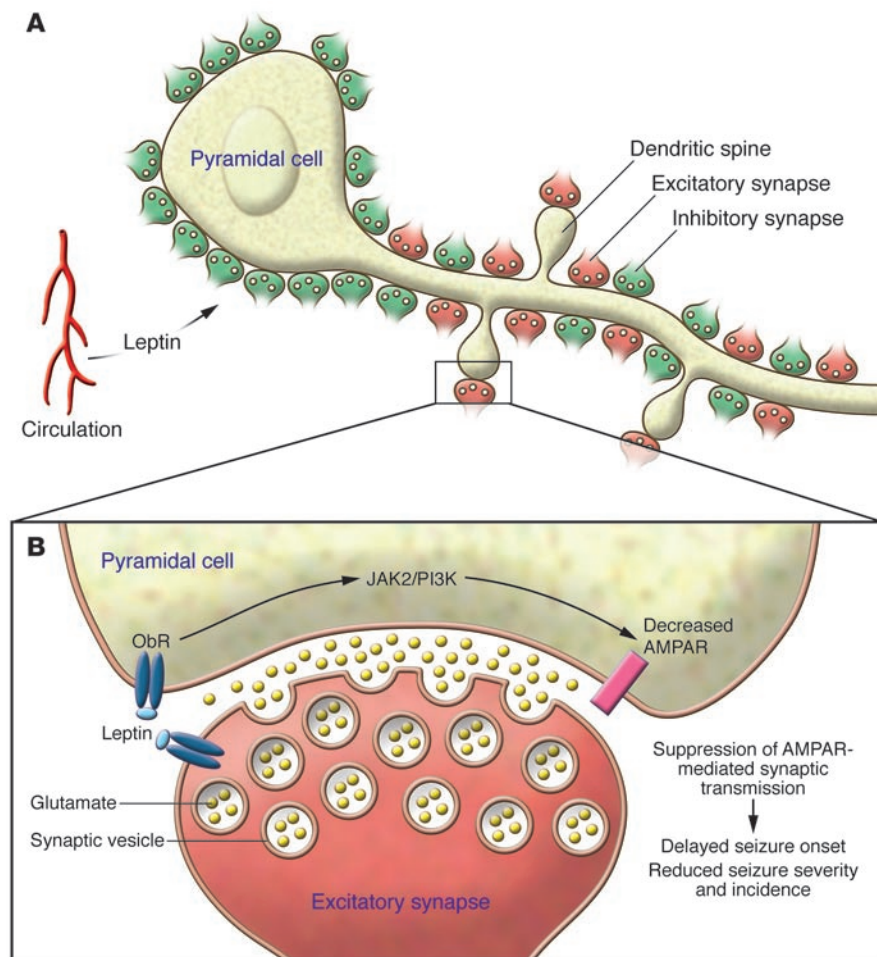
**Nonstandard abbreviations used:** AMPA,  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid.

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Over the last century, it has been hypothesized and then experimentally proven that a humoral signal from the periphery, specifically from adipose tissue, plays a role in the regulation of feeding and energy metabolism (1–5). The identity of this hormone,

named leptin, was elegantly revealed by Friedman and colleagues in 1994 (6), and thus began a new era in the use of molecular biology in the quest to identify a cure for metabolic disorders, most notably obesity. This discovery revolutionized the field and attracted increasing numbers of creative researchers with sophisticated tools in an effort to determine the mechanisms of action of leptin in the hypothalamus and its role in the regulation of feeding and adiposity (reviewed in ref. 7). To date, despite the great wealth of knowledge that has been gained and the discovery of new hormones, no leptin-based medical remedy has emerged for the treatment of obesity. While new avenues of research in this area are being pursued by many, the study by Xu et al. reported in this issue of the *JCI* (8) reveals that the leptin signaling pathway has important functions that go beyond

**Figure 1**

Schematic illustration of the anticonvulsant effect of blood-borne leptin on hippocampal principal cells. **(A)** Leptin derived from the circulation targets pyramidal cells of the hippocampal formation that are innervated by excitatory (red) and inhibitory (green) synapses. Excitatory synapses are frequently established on dendritic spines of pyramidal cells. **(B)** The report by Xu et al. (8) in this issue of the *JCI* shows that intranasal leptin administration in two rodent seizure models has an anticonvulsant effect. The effect of leptin on synaptic transmission in the hippocampus involves leptin binding to its receptor, followed by activation of JAK2/PI3K signaling pathways induced by the long form of the leptin receptor (ObR), which alters both pre- and postsynaptic mechanisms and leads to suppression of glutamate-induced excitatory postsynaptic events mediated by AMPA-type glutamate receptors (AMPA). This suppressed excitatory neurotransmission explains leptin's anticonvulsant effects.

its role in the regulation of food intake and metabolism. In their study, these authors describe the mechanisms of action of leptin in the hippocampus and show that leptin opposes the propagation of seizures in two rodent seizure models. They demonstrate that this effect can be achieved by nasal administration of the hormone, thereby strengthening the potential for the use of leptin in anticonvulsant therapies.

### Current epilepsy therapeutics

The cause of epilepsy varies among patients and involves various brain structures. Temporal lobe epilepsy is related to malfunctioning of excitatory neurotransmission of the hippocampal formation. While surgery may be an option when the brain region responsible for seizure generation has been identified and is responsible for no vital functions, the most commonly used therapeutic approach to control seizures is pharmacological. The majority of the pharmaceutical compounds available to treat epilepsy target neurotransmitter systems

in an effort to slow excitatory, glutamate transmission either by directly antagonizing glutamate receptors or enhancing the tone of the inhibitory neurotransmitter GABA (9). Because glutamate and GABA are ubiquitous neurotransmitters throughout the CNS, the side effects of these therapies involve a broad array of brain mechanisms, from the regulation of homeostasis to alterations in higher brain functions. Thus, new candidate epilepsy therapeutics would ideally selectively target molecules with restricted distribution in the brain, which may reduce side effects that have an impact on other brain functions. Leptin receptors are not ubiquitous in the brain; however, they are expressed in the hippocampal formation (10).

### Action of leptin on seizures

Xu et al. (8) tested leptin's anticonvulsant action in two rodent seizure models either by directly injecting leptin into the cortex or by intranasal administration (Figure 1). They found that focal seizures induced by

neocortical injections of 4-aminopyridine (4AP) in rats were shortened and reduced in number by coinjection with leptin. In addition, leptin reduced neuronal spiking in an *in vitro* seizure model. In mice, intranasal administration of leptin produced elevated brain and serum leptin levels and delayed the onset of pentylenetetrazole-induced generalized convulsive seizures. In identifying the underlying mechanism, leptin was found to inhibit ionotropic  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) glutamate receptor-mediated synaptic transmission in hippocampal slices (Figure 1B). This inhibition was found to be leptin-receptor dependent, as leptin failed to inhibit synaptic responses in slices from leptin receptor-deficient *db/db* mice. This study reveals that, in agreement with previous findings on leptin's effect on the hippocampus and seizures (11), it is the JAK2/PI3K pathway (leptin is known to signal through its receptor by activating JAK/STAT and JAK2/PI3K pathways) that is likely to be involved, as Xu et al. show



that JAK2 and PI3K antagonists prevented leptin inhibition of AMPA receptor-regulated synaptic transmission (Figure 1). In light of the results of Xu et al. (8) and earlier observations that leptin levels may be increased during consumption of a ketogenic diet (12), it is plausible that leptin-triggered signaling may play a role in the known beneficial effects of a ketogenic diet on suppression of seizures (13).

### The hippocampus is more than a seizure-controlling device

The elaboration of the molecular mechanism through which leptin alters AMPA receptor activity is an important addition to our understanding of how leptin can affect hippocampal synaptic transmission during physiological and pathological conditions. However, there are many questions that need to be addressed before a true sense of the usefulness of leptin can be assessed regarding therapies for epilepsy. First, the rodent models tested by Xu et al. (8) are acute models of seizure generation, and seizures were generated in the face of elevated leptin levels either via cortical or nasal application of the hormone. In almost all cases of epilepsy, patients are identified and treated *after* the first episode of a seizure has occurred. Thus, it will be important to determine whether, in chronic seizure models, post hoc administration of leptin specifically via the nasal route will have beneficial effects. An equally intriguing aspect of leptin action is its inability to affect brain functions associated with food intake and energy expenditure in diet-induced obese animals. This so-called *leptin resistance*, may occur due to changes in blood-brain barrier function (reviewed in ref. 14) and/or intraneuronal events (15), and it will be important to determine whether this resistance also emerges in the hippocampus. This is specifically significant, as the human population, most alarmingly children, is becoming more overweight and moving toward an increased likelihood of leptin resistance. The data acquired and knowledge gained from the utilization of available animal models will be vital in order to determine the viability of potential therapies.

Suppression of glutamate transmission by leptin can diminish the likelihood of seizure generation and propagation. The

flip side of the coin is that this same glutamate-regulated synaptic transmission in the hippocampus is critical for spatial learning and memory. If leptin were to be considered as a putative epilepsy therapy, an intriguing option would be to determine to what extent the suppression of hippocampal synaptic events by leptin might interfere with learning and memory. Furthermore, as mentioned above, the US and most Western societies are experiencing a trend of increasing body mass index, which is associated with increasing circulating leptin levels. Whether increasing levels of leptin in the circulation would have an overall negative impact on higher brain functions or would be irrelevant due to leptin resistance are important questions to entertain in light of recent studies showing the U-shaped nature of the dose-response curve of leptin in hippocampal function, in which high doses of leptin impair spatial learning and memory performance (16, 17).

Undoubtedly, the potential of leptin to suppress initiation and propagation of seizures could fill a critical medical need. Clinically, the most significant message of the study by Xu et al. (8) is the hope for the possibility of interfering with seizure initiation and propagation by leptin via an intranasal route of application. Should the approach be feasible and effective in humans, a new therapy could rapidly be on the way. Equally intriguing is the trend of moving the focus on therapeutic potentials for metabolic hormones, such as leptin and ghrelin, from classical metabolic disorders, such as obesity and diabetes, to higher brain functions (18) and neurodegenerative disorders of the brain, including epilepsy. In light of the emerging recognition of the critical role of impaired cell metabolism in most of these disorders (19), the future may hold greater promise for therapeutic success using metabolic hormones and their signaling modalities to combat neurodegenerative disorders rather than obesity.

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