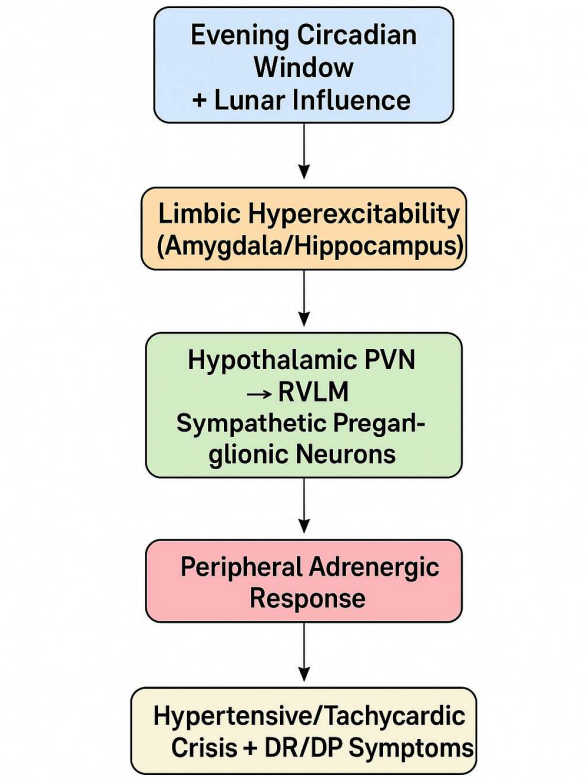
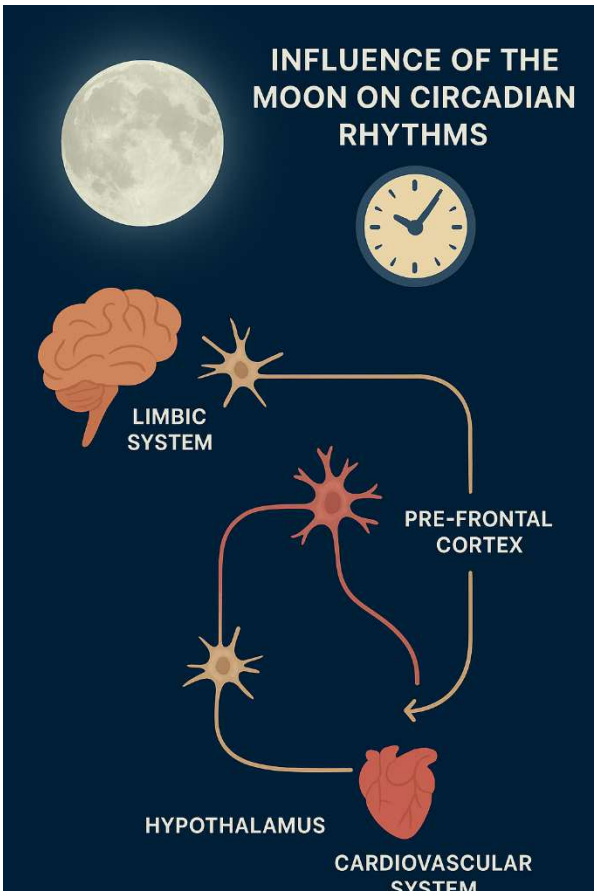
Integrated Limbic–Autonomic Kindling Model with Circadian and Lunar Modulation: Pathophysiological Analysis and Clinical Application in a Case of Nocturnal Hypertensive Crises





Abstract

We present a clinical case of a previously normotensive adult who developed paroxysmal nocturnal hypertensive episodes associated with panic symptoms, depersonalization/derealization, and tachycardia, with clear circadian periodicity (21:00–23:00 hours) and temporal correlation with full-moon phases. The favorable response to low-dose levetiracetam suggests an underlying limbic hypersensitivity mechanism of the kindling type, capable of inducing micro-convulsive discharges with significant autonomic impact. We propose an integrative model that articulates limbic–hypothalamic dysfunction, autonomic dysregulation, circadian vulnerability and lunar modulation as interdependent elements within

a multisystemic syndrome. This approach provides a conceptual foundation for future research in clinical neuro-chronobiology.

1. Introduction

Neurobiological phenomena that regulate human behavior operate at multiple levels—from subcortical circuits to biological rhythms that span different temporal scales. While the clinical importance of circadian rhythms (~24 h) is widely recognized, accumulating evidence indicates that monthly rhythms and astronomical phenomena, such as lunar variations, also influence neuroendocrine, autonomic and behavioral parameters.

Concurrently, the kindling phenomenon—well studied in epileptogenesis—describes progressive sensitization of neural networks after repeated subthreshold stimuli, producing a state of hyperexcitability without the need for overt motor convulsive activity. When this sensitization occurs in limbic circuits, manifestations may include intense affective, perceptual and autonomic phenomena.

The case presented enables construction of an integrative pathophysiological model that unites:

1. limbic hyperexcitability of the kindling type,
2. hypothalamic autonomic dysregulation,
3. nocturnal circadian vulnerability,
4. possible electromagnetic lunar modulation.

2. Case Presentation

An adult patient without relevant cardiovascular history and with baseline normotension/hypotension had long-standing panic attacks previously managed with monoamine oxidase inhibitors (MAOIs), benzodiazepines and propranolol, with relative stability.

Suddenly, the patient began experiencing nocturnal episodes of severe hypertension (up to **190/110 mmHg**) accompanied by tachycardia (≈100 bpm), a sensation of impending death, derealization and depersonalization. These episodes consistently clustered between **21:00 and 23:00 hours**, and retrospective analysis showed aggregation during full-moon periods.

Initial management required clonidine, selective β1-blockers, amlodipine 5 mg TID and sublingual nifedipine as rescue. Suspecting limbic hyperexcitability, **levetiracetam 125 mg TID** was added; nocturnal crises progressively resolved, blood pressure returned to baseline levels

(≈**90/60 mmHg**) and amlodipine was discontinued due to pretibial edema. The patient remained on occasional atenolol as needed.

3. Integrated Pathophysiology

3.1 Limbic kindling and non-motor micro-convulsive activity

The limbic system—particularly the amygdala and hippocampus—contains excitatory networks prone to sensitization. Repeated panic episodes or emotional stress can induce kindling, lowering activation thresholds and facilitating:

- subclinical microelectrical discharges,
- abrupt eruptions of fear or "impending death,"
- perceptual phenomena such as depersonalization and derealization,
- sudden autonomic activation.

These discharges are equivalent to "limbic micro-seizures": they lack motor involvement but exert large autonomic effects.

3.2 Amygdala–Hypothalamus–Autonomic axis

Hyperactivated amygdala projects to:

- the paraventricular nucleus of the hypothalamus (PVN),
- the rostral ventrolateral medulla (RVLM),
- preganglionic sympathetic neurons.

The result is a sympathetic «burst»: increased vasoconstrictor tone, tachycardia and adrenal catecholamine release—explaining the observed paroxysmal hypertensive crises.

3.3 Circadian vulnerability and nocturnal sympatho-vagal imbalance

Late-night physiology is characterized by:

- reduction in vagal tone,
- fluctuations in melatonin and cortisol,
- changes in thermoregulation and blood pressure,
- greater lability of specific hypothalamic nuclei.

This physiological milieu may facilitate clinical expression of already-sensitized neural networks.

3.4 Monthly rhythms and lunar modulation

Various disciplines (chronobiology, botany, geophysics) have documented effects of lunar phases on:

- sleep–wake cycles,
- melatonin secretion,
- patterns of electromagnetic activity,
- tissue fluid dynamics.

The correlation between full moon and crisis onset suggests that small electromagnetic or gravitational changes could modulate the limbic excitability threshold, acting as triggers in vulnerable individuals.

3.5 Role of levetiracetam

Levetiracetam acts on synaptic vesicle protein SV2A, reducing excessive glutamate release and stabilizing excitatory homeostasis. Its efficacy in this case supports the hypothesis of a subconvulsive limbic mechanism.

4. Syndromic Proposal: "Limbic–Autonomic Kindling Syndrome with Circadian and Lunar Modulation"

We propose a multisystem syndrome characterized by:

Limbic component
Kindling-type hyperexcitability; microdischarges; depersonalization/derealization; paroxysmal fear.

Autonomic component
Sympathetic storms; nocturnal hypertensive crises; tachycardia.

Endocrine–circadian component
Alterations in nocturnal transition; melatonin/cortisol changes.

Chronobiological (lunar) component
Periodic lowering of neuronal excitability threshold during full moon phases.

The clinical course and therapeutic response justify considering this syndrome as a coherent pathophysiological entity.

5. Discussion

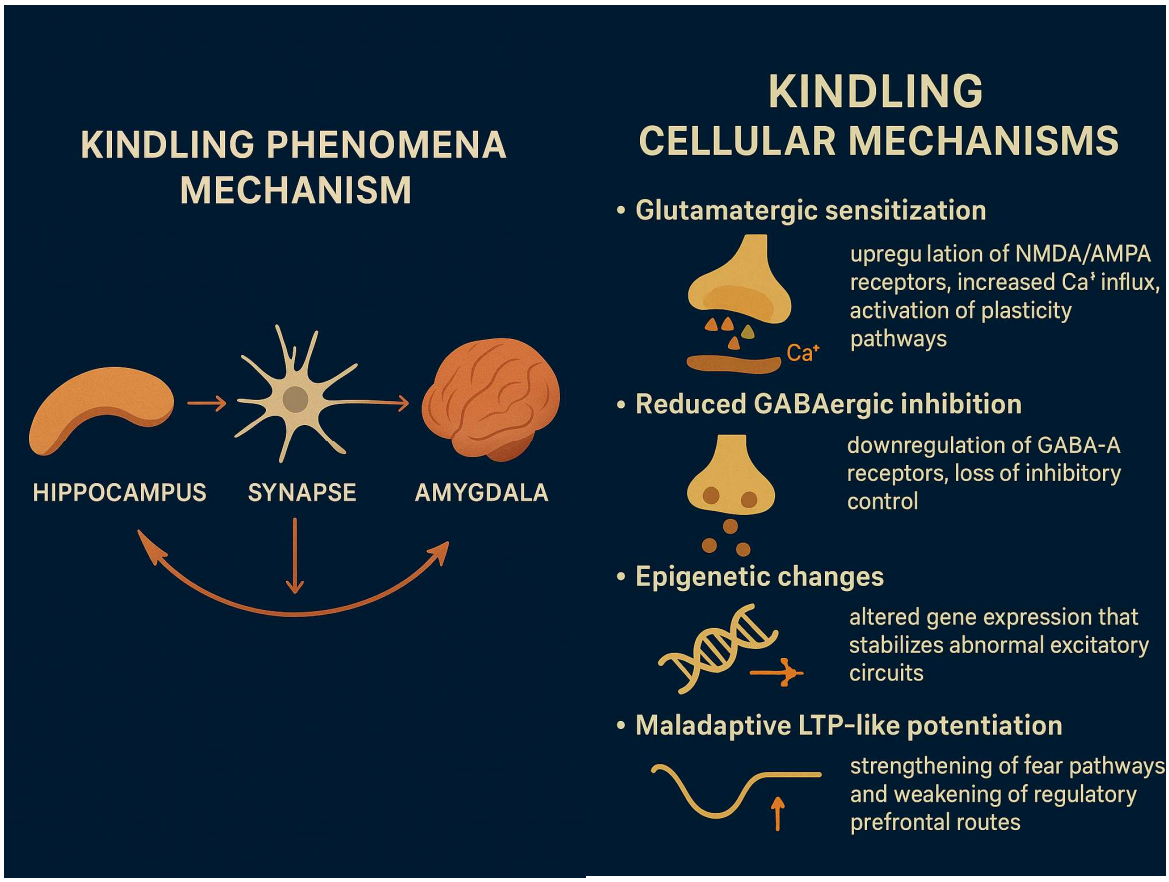
This case prompts reflection on several relevant points:

1. **Kindling is not exclusive to epilepsy.**
   It can manifest as intense affective and autonomic phenomena without motor convulsions.
2. **The boundary between "psychiatric" and "neurological" is porous.**
   Limbic discharges can mimic panic, producing mixed neuro cardio vascular presentations.
3. **Reported periodicity merits serious consideration.**
   Circadian and lunar rhythms, though understudied clinically, influence human physiology more than traditionally acknowledged.
4. **Levetiracetam may be useful in subgroups with limbic hyperexcitability.**
   Particularly when autonomic paroxysms are refractory to benzodiazepines or beta-blockers.
5. **An integrative model improves diagnostic precision.**
   Incorporating neurophysiology, endocrinology and chronobiology reduce the tendency to attribute such presentations solely to psychological causes.

Conclusions

The presented case exemplifies a complex phenomenon in which limbic hyperexcitability (kindling) interacts with autonomic mechanisms, circadian vulnerability and lunar modulation. Resolution of crises with levetiracetam supports a neuroelectric, subconvulsive etiology rather than a primary cardiologic disorder. This integrative model offers a useful framework for understanding mixed limbic–autonomic paroxysmal syndromes and suggests avenues for future research in clinical neuro-chronobiology.

THE KINDLING PHENOMENON: A DETAILED, MULTISYSTEM AND CLINICALLY APPLIED REVIEW



The kindling phenomenon is a key neurobiological process that explains how the nervous system becomes progressively sensitized by repeated stimuli, eventually generating persistent neuronal hyperexcitability even in the absence of the initial trigger. Originally discovered in epilepsy research, its clinical relevance now extends across neuropsychiatry, autonomic physiology, stress, panic disorders and certain dysautonomia syndromes.

1. Origin of the concept

Graham Goddard (1967) showed that:

- Subthreshold electrical stimuli that by themselves did not evoke seizures,

- when repeated daily,
- could generate full epileptic discharges after weeks,
- and continue to occur even without the original stimulus.
  This progressive sensitization resembles “kindling a fire,” hence the term.

2. Fundamental characteristics

2.1 Progressive sensitization
The same stimulus intensity produces increasingly larger responses. Instead of adaptation, there is potentiation.

2.2 Threshold reduction
Over time the nervous system requires less stimulus to activate; minimal triggers (emotional states, hormonal changes, temperature shifts, or circadian factors) can provoke crises.

2.3 Circuit autonomy (self-sustained activity)
After sufficient sensitization the neuronal circuit remains hyperexcitable and can continue generating seizures, panic attacks, tachycardia, hypertensive paroxysms, or depersonalization/derealization even when the original trigger is removed.

3. Neuroanatomical loci of kindling

Although inducible in multiple structures, the most susceptible are:

1. **Amygdala** — emotional fear center; triggers autonomic responses; rich in glutamatergic plasticity.
2. **Hippocampus** — contextual memory and emotional regulation; networks sensitive to chronic stress.
3. **Medial prefrontal cortex** — normally inhibits amygdala; when compromised, loss of top-down control.
4. **Hypothalamus (PVN)** — direct gateway to sympathetic activation and cardiovascular responses.
5. **Brainstem (RVLM, locus coeruleus)** — presympathetic centers that amplify autonomic discharge.

4. Cellular mechanisms

Kindling is sustained by durable plastic changes:

- **Glutamatergic sensitization**: upregulation of NMDA/AMPA receptors, increased Ca^{2+} influx, activation of plasticity pathways.
- **Reduced GABAergic inhibition**: downregulation of GABA-A receptors, loss of inhibitory control.
- **Epigenetic changes**: altered gene expression that stabilizes abnormal excitatory circuits.
- **Maladaptive LTP-like potentiation**: strengthening of fear pathways and weakening of regulatory prefrontal routes.

5. Limbic kindling: clinical relevance

Limbic kindling does not produce motor convulsions but causes affective and autonomic symptoms: sudden panic attacks, sensations of imminent death, derealization/depersonalization, stress hypersensitivity, abrupt sympathetic discharge, nocturnal paroxysmal hypertension, sudden tachycardia, sweating, tremor, nausea. This explains many "mixed" crises with psychiatric appearance but underlying neuroelectrical components.

6. Interaction with the autonomic system

Pathway: **Hyperexcitable amygdala → hypothalamic PVN → RVLM → sympathetic neurons → heart and vessels**, producing increased noradrenaline, vasoconstriction, hypertensive peaks, tachycardia and nighttime attacks. Nighttime physiology increases vulnerability.

7. Kindling and circadian rhythms

Kindling expression is favored during sleep–wake transitions, melatonin nadirs, nocturnal autonomic tone shifts and sympatho-vagal imbalance. Hence many episodes occur between 21:00–02:00.

8. Lunar influence on a hyperexcitable network

Innovative point: studies report reduced melatonin at full moon, decreased deep sleep, increased micro-awakenings, detectable cellular oscillations related to lunar electromagnetic fields, and increased emotional reactivity in animals. In an already sensitized network, such changes can act as additional triggers.

9. Why levetiracetam works in limbic kindling

Levetiracetam targets SV2A, modulates glutamate release, stabilizes excitatory synapses, and raises limbic firing thresholds. It reduces micro discharges, hyperexcitability, autonomic crises, panic attacks, depersonalization/derealization phenomena and hypertensive spikes. Its efficacy in the described case supports the model.

10. Conclusion

Kindling is a process of progressive neuronal sensitization, especially in the limbic system, producing intense affective and autonomic symptoms. It interacts with circadian and lunar rhythms, explains nocturnal crises and panic, and responds to stabilizers such as levetiracetam. The model you are developing is robust, integrative and has publication potential because it links neurophysiology, endocrinology, chronobiology, psychiatry and autonomic cardiology.