Mechanism of Thyrotoxic Periodic Paralysis

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ABSTRACT

The pathogenesis of thyrotoxic periodic paralysis has long been thought related to increased Na⁺–K⁺ ATPase activity stimulated by thyroid hormone and/or hyperadrenergic activity and hyperinsulinemia. This mechanism alone, however, cannot adequately explain how hypokalemia occurs during acute attacks or the associated paradoxical depolarization of the resting membrane potential. Recent findings that loss of function mutations of the skeletal muscle-specific inward rectifying K⁺ (Kir) channel, Kir2.6, associate with thyrotoxic periodic paralysis provide new insights into how reduced outward K⁺ efflux in skeletal muscle, from either channel mutations or inhibition by hormones (adrenergic or insulin), can lead to a vicious cycle of hypokalemia and paradoxical depolarization, which in turn, inactivates Na⁺ channels and causes muscle unexcitability and paralysis.


Muscle weakness progressing to paralysis caused by hypokalemia is a potential life-threatening but reversible medical emergency. Hypokalemic muscle paralysis can result from renal or gastrointestinal loss of K⁺ or shift of K⁺ into cells induced by acid–base disturbances or stimulated by drugs or endogenous hormones.¹

Hypokalemic periodic paralysis (HypoPP) is a heterogeneous group disorder portraying episodic muscle weakness associated with hypokalemia from acute shift of K⁺ into cells unrelated to known acid–base disorders or exogenously administered substances. The causes of HypoPP may be familial, which is more common among non-Hispanic Caucasians, and predominantly caused by mutations in the Cav1.1 skeletal muscle voltage-gated Ca²⁺ channel or the Na⁺,1,4 Na⁺ channel. Nonfamilial HypoPP includes thyrotoxic periodic paralysis (TPP) and sporadic periodic paralysis (SPP), which are more common among Asians and Hispanics.² Although the incidence of TPP in Asian countries (2%) is approximately 10–20 times higher than the incidence in non-Asian ethnic populations (0.1%–0.2%), TPP is increasingly reported in Western countries because of globalization and immigration.³

DIAGNOSIS AND MANAGEMENT OF TPP

TPP characterized by a triad of muscle paralysis, acute hypokalemia without total body K⁺ deficit, and hyperthyroidism is not only a neurologic and endocrinological emergency but also quite interesting to nephrologists. It is fraught with diagnostic and therapeutic challenges. Rapid recognition and termination of TPP is mandatory to avoid potentially fatal complications from severe hypokalemia. Patients with TPP often have subtle symptoms related to hyperthyroidism.³ Assessment of thyroid function is also often not immediately available. Furthermore, acute discovery of thyrotoxicosis and hypokalemia does not always make the diagnosis of TPP; patients with hyperthyroidism may have chronic hypokalemia associated with the use of diuretics, laxative, mineralocorticoid excess state, or concurrent renal tubular disorders such as renal tubular acidosis or Bartter’s or Gitelman’s syndrome.

An assessment of renal K⁺ excretion and acid–base status at presentation as well as the amount of KCl required to correct hypokalemia are very helpful in diagnosing TPP. Several clinical and laboratory findings are characteristic of TPP (Table 1).³,⁴ Regarding acute therapy, the dose of KCl should be minimal to avoid rebound hyperkalemia, and nonselective β-blockers may be the alternative choice, especially for those patients who developed hypokalemia associated with an evidence of hyperadrenergic activity.⁵ The goal of chronic therapy in TPP is to normalize thyroid function and avoid the precipitating factors for acute attack.

PATHOGENESIS OF HYPOKALEMIA IN TPP

The pathogenesis of TPP has remained largely mysterious for decades since the discovery of the first case in early 20th century. Acute hypokalemia is the
principle laboratory finding, and it correlates with the severity of paralysis. Normalization of serum K⁺ levels leads to recovery of muscle strength. Skeletal muscle is the largest single pool of total body K⁺ stores, and it plays an important role in extracellular K⁺ homeostasis. In the skeletal muscle, Na⁺−K⁺ ATPase and K⁺ channels, including inward rectifying K⁺ (Kir) and delayed rectifying K⁺ channels, provide the main access for inward and outward K⁺ movements, respectively. It is estimated that active uptake of K⁺ through Na⁺−K⁺ ATPase at a rate of 125 mmol/min can decrease serum K⁺ concentration by 3 mM within 1 minute, providing that there is no concomitant K⁺ efflux from myocytes. The critical role of myocyte K⁺ efflux in extracellular K⁺ homeostasis is supported by the finding that patients with barium (an inhibitor of skeletal muscle K⁺ channels) poisoning develop acute hypokalemia and muscle paralysis.

The important role of Na⁺−K⁺ ATPase pumps in the pathogenesis of TPP is supported by the finding that their activity in the skeletal muscle is significantly increased. Thyroid hormone can stimulate Na⁺−K⁺ ATPase in skeletal muscle by genomic mechanism, acting on the thyroid hormone responsive elements to upregulate the transcription of the gene encoding Na⁺−K⁺ ATPase, and through nongenomic mechanisms by enhancing the intrinsic activity or promoting membrane insertion of the pump. Hyperthyroidism can also enhance the stimulation of pump activity by β₂-adrenergic agonists by amplifying the production of intracellular cAMP. Hyperinsulinemia is also observed in acute attack of TPP, and the release of insulin in response to oral glucose challenge is exaggerated in TPP patients, supporting the idea that insulin participates in the pathogenesis of hypokalemia in TPP.

Insulin induces cellular K⁺ shifts by stimulating the intrinsic activity or membrane insertion of Na⁺−K⁺ ATPase. The effect of insulin may account for the observation that a high-carbohydrate diet can be a precipitating factor for TPP. Sympathetic stimulation of insulin release in pancreas β-cells provides additional rationale for using nonselective β-blockers to treat acute hypokalemia and paralytic attack of TPP. TPP is also known to occur predominately among males despite a higher incidence of thyrotoxicosis in women, suggesting the potential role of androgen on Na⁺−K⁺ ATPase activity. Although more work needs to be done in this area, androgens may increase Na⁺−K⁺ ATPase activity through androgen receptor and hyperadrenergic state. The traditional mechanisms of Na⁺−K⁺ ATPase activation in TPP are shown in Figure 1A.

Activation of Na⁺−K⁺ ATPase cannot be the only mechanism for TPP, because only a minority (~2%) of patients with hyperthyroidism develop hypokalemic paralysis. By itself, the increased Na⁺−K⁺ ATPase activity in muscle may be compensated by increased K⁺ efflux, limiting its impact on the extracellular K⁺ homeostasis and the extent of hypokalemia; indeed, the total intracellular K⁺ content measured in the diaphragm muscle of a thyrotoxic mouse is unchanged from the normal. Thus, additional factors such as decreased K⁺ efflux must be at play to cause clinically significant hypokalemia. Studies have shown that the outward K⁺ current is decreased in intercostals muscle fibers of both patients with TPP and familial HypoPP. Moreover, insulin and catecholamine not only activate Na⁺−K⁺ ATPase but also inhibit Kir channels.

Two recent studies report that mutations in the gene encoding Kir2.6, a skeletal muscle-specific Kir channel, are associated with TPP and predispose these patients to acute paralytic attacks. In a report by Ryan et al., the prevalence of Kir2.6 mutation was up to 33% in Caucasians and Brazilians. Thyroid hormone upregulates the transcription of Kir2.6 through an upstream thyroid hormone responsive element in the promoter region of channel gene. In the other report, Cheng et al. found three additional loss of function mutations in Kir2.6 channels in patients with TPP as well as SPP. The work by Cheng et al. also reported that Kir2.6 forms functional homotetramer and heterotetramer with Kir2.1, another Kir channel in the skeletal muscle. Kir2.6 mutants exert a dominant negative effect on both WT Kir2.1 and Kir2.6 channels.

Overall, these two recent papers provide compelling support for the role of genetic mutations in Kir2.6 channel in the pathogenesis of TPP. Loss of function of Kir2.6 together with increased activity of Na⁺−K⁺ ATPase may trigger a positive feed-forward cycle of hypokalemia, leading to paradoxical depolarization with consequent inactivation of Na⁺ channel and muscle inexcitability (Figure 1B).

## Table 1. Distinct clues for the diagnosis of TPP

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<th>Clues</th>
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<tr>
<td>A. Sex: adult males</td>
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<td>B. History: nonfamilial paralysis</td>
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<td>C. Clinical symptoms and signs</td>
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<td>D. Electrocardiographic findings</td>
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<td>E. Electromyographic findings</td>
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<tr>
<td>F. Blood and urine electrolytes and acid-base</td>
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<td>G. Less K⁺ dose to achieve recovery</td>
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<td>H. Normal or increased serum calcium</td>
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<td>I. Thyroid hormone-responsive element</td>
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<tr>
<td>J. Hyperinsulinemia</td>
</tr>
<tr>
<td>K. Hypophosphatemia</td>
</tr>
<tr>
<td>L. Hyperparathyroidism</td>
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<tr>
<td>M. Increased serum phosphate excretion</td>
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<tr>
<td>N. Paradoxic depolarization</td>
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**MUSCLE PARALYSIS ASSOCIATED WITH HYPOKALEMIA-INDUCED PARADOXICAL DEPOLARIZATION IN TPP**

Based on the Nernst equation \( E = -58 \) mV \( \times \log \left[ \frac{[K^+]_{in}}{[K^+]_{out}} \right] \), the resting membrane potential should hyperpolarize when extracellular K⁺ decreases. However, muscle fibers from patients with HypoPP depolarize under low extracellular K⁺ conditions (~3 mM). This
hypokalemia-induced paradoxical depolarization of the resting membrane potential leads to inactivation of Na\(^+\) channels, rendering them unexcitable, and it is central to pathophysiology of skeletal muscle paralysis in HypoPP.\(^{12,16}\) In familial HypoPP, paradoxical depolarization is caused by mutations in the voltage sensor of Nav1.4 and Cav1.1 channels giving rise to aberrant gating pore currents and imbalance between inward leak current and outward K\(^+\) current.\(^{15,16}\) In TPP, reduced outward K\(^+\) current because of loss of function mutations causes a similar imbalance between inward leak current and outward K\(^+\) current, and it results in paradoxical depolarization.\(^{15}\)

CONCLUDING REMARKS

Recent studies provide new insights into the pathogenesis of nonfamilial HypoPP, TPP, and SPP. Many questions, such as the causes of TPP in patients without mutations in the coding region of Kir2.6 and voltage-gated Na\(^+\) and Ca\(^{2+}\) channels, remain. Although it remains to be studied, reduced expression of Kir2.6 channel protein from mutations in the noncoding region of the channel gene or inhibition of the channel by endogenous factors, such as insulin or catecholamine, or exogenous factors, such as caffeine alone or combined, may lead to periodic paralysis in patients without known mutations in Kir2.6 and voltage-gated Na\(^+\) and Ca\(^{2+}\) channels. New perceptions regarding the pathogenesis of TPP will be important in understanding overall extracellular K\(^+\) homeostasis and the therapeutic approaches to hypokalemic paralysis.

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DISCLOSURES

None.

REFERENCES


Figure 1. Mechanism of TTP. (A) A traditional pathogenesis of TPP. An increased Na\(^+\) – K\(^+\) ATPase activity directly induced by thyroid hormone and indirectly induced by hyperadrenergic activity, hyperinsulinemia, and androgen is mostly involved. The open circle denotes the skeletal muscle cells and Na\(^+\)/H\(^+\) exchanger (NHE). (B) Reduced K\(^+\) channel efflux in TPP. The enhanced Na\(^+\) – K\(^+\) ATPase activity causes initial hypokalemia, and the reduced outward Kir current caused by hypokalemia, loss of function mutation, or hormone (adrenalin or insulin) -mediated inhibition on Kir channels can potentially inhibits total K\(^+\) efflux, leading to the trapping of K\(^+\) in the cell; a vicious cycle of hypokalemic-induced paradoxical depolarization and an inactivation of Na\(^+\) channel with muscle inexcitability and paralysis can result.