PHYSIOLOGY & MEMBRANE BIOLOGY

SCHOOL OF MEDICINE

UNIVERSITY OF CALIFORNIA AT DAVIS

DISTINGUISHED SPEAKER SERIES

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"Modulation of potassium channels by free heme and heme degradation products"

Heme is traditionally thought of as a stable protein cofactor, as exemplified in hemoglobin, myoglobin and guanylyl cyclase. In contrast to this traditional view, recent studies show that free heme may be a diffusible signaling molecule capable of acutely regulating functions of many proteins. One of the heme signaling targets is the large-conductance calcium- and voltage-gated Slo1 BK channel expressed numerous tissues. Allosteric gating of the tetrameric Slo1 BK channel encompassing the gate, voltage sensors and cytoplasmic divalent cation sensors is profoundly altered by binding of heme to the cytoplasmic carboxyl terminus. Because heme is a modulator of the allosteric gating mechanism, heme stimulates the channel activity under some circumstance but inhibits under others. The Slo1 BK channel is also modulated by carbon monoxide (CO), one of the degradation products of heme. CO is a deadly poison but at low concentrations it is a putative gaseous messenger. CO directly stimulates the Slo1 BK channel and the effect requires one of the two high-affinity calcium sensors of the channel. The CO-sensitive calcium sensor is also required for the stimulatory action of cytoplasmic proton. The findings further illustrate the wide modulatory repertoire of the Slo1 BK channel. .

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