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**A BIOPHYSICAL PERSPECTIVE ON DIABETIC NEUROPATHY:
THE ROLE OF THE REACTIVE METABOLITE METHYLGLYOXAL**

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More than 220 million people are currently affected by diabetes worldwide, and 50% of them display neuropathic complications (diabetic neuropathy). Most attempts to explain the cause of diabetic neuropathy focused on a central role of hyperglycemia. However, recent clinical studies have shown that normalization of glycemia in type 2 diabetic patients does not lead to significant attenuation of neuropathic symptoms (spontaneous pain, abnormal thermal sensitivity, autonomic dysfunction). Moreover, in most cases neuropathic symptoms precede the clinical detection of elevated glycemia. Therefore, the hypothesis that neuropathy is induced following microvasculature lesions of vasa nervorum due to hyperglycemia has to be reconsidered. Recent clinical studies have demonstrated an increase in the plasma level of the reactive metabolite methylglyoxal in diabetic patients with neuropathic symptoms. We show that this metabolite depolarizes cultured sensory neurons, and increases their excitability via a post-translational modification of the voltage gated TTX-resistant sodium channel Nav1.8 which potentiates channel activity. Cultured sensory neurons from Nav1.8-deficient (Nav1.8^{-/-}) mice are also depolarized in the presence of methylglyoxal, but, in contrast to wild type animals, this does not render them hyperexcitable. Our results indicate a pro-algesic role of methylglyoxal and may explain the initiation and maintenance of painful episodes associated with diabetic neuropathy.