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Dissertation

Title *The role of glutamate signaling pathway in diabetic neuropathy*

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Abstract

The majority of diabetics develop neuropathy, which can be debilitating, but the underlying pathophysiological mechanisms are poorly understood. Diabetic neuropathy progresses in a distal to proximal manner. Previous studies have shown that glutamate, the most common excitatory neurotransmitter, plays a role in the pathogenesis of neuropathy. The reason why the role of glutamate in nociception becomes a problem in diabetes and the mechanisms that are involved are unknown. Based on the preliminary data, the hypothesis was that glutamate pathways are likely to be involved in diabetic neuropathy particularly neuropathic pain. Pathways were investigated to look for changes that might reflect neuropathic pain and fit with previously established pharmacological evidence. The aim of this project was to identify changes in expression of genes and their protein products that are involved in glutamate signalling in diabetes. This will help to further the understanding of the mechanisms of diabetic neuropathy. In diabetic rats, there were consistent changes in expression, particularly in the lumbar and sacral dorsal root ganglia of the spinal cord and in the sympathetic ganglia. The changes were consistent between the different groups of animals as well as between adjacent groups of ganglia. The most prominent changes in both the GK groups included marked upregulation of Gria4 (ionotropic AMPA receptor), downregulation of Grik3 and Grik4 (both ionotropic, kainite receptors) and Grin1 and Grin2A (both ionotropic, NMDA receptors), activation of all of which has been shown to induce hyperalgesia; downregulation of Slc1a6 (excitatory amino acid transporter 4) and upregulation of Slc1a1 (excitatory amino acid transporter 3), both of which mediate neural reuptake of glutamate from the synaptic cleft; and upregulation of Gclc (glutathione synthase), which reflects a response to protect against oxidative damage.
Despite many theories existing about the pathogenesis of diabetic neuropathy, there is no unifying hypothesis. It is possible that changes in glutamate signalling can contribute to these other mechanisms and possibly unify these different theories. A better understanding of the role that glutamate plays in development of diabetic neuropathy may pave the way for future therapeutic intervention.

Keywords: Diabetes, Diabetic Neuropathy, Glutamate Signalling, Dorsal Root Ganglia, Sympathetic Ganglia.

Research Relevance and Potential Impact

Neuropathy affects more than 50% of diabetics but the underlying pathophysiological mechanism remains poorly understood. The symptoms and signs can range from mildly irritating to debilitating, depending on the system of the body affected. Glutamate is the most common type of excitatory neurotransmitter in the mammalian nervous system. Its receptors are broadly classified as slow acting metabotropic and fast acting ionotropic. Studies show that disturbance in neural glutamate signalling plays a role in the pathogenesis of several neurodegenerative and neuropathic disorders. Several glutamate receptor subtypes are known to mediate peripheral nociceptive transmission while their respective receptor antagonists can alleviate neuropathic pain. Reduction in the local production and release of glutamate from nerve terminals also alleviates allodynia, hyperalgesia, and thermal sensitivity in diabetic animals and shows therapeutic promise. While glutamate signalling appears to contribute to the development of diabetic neuropathy, the reason why its role in nociception becomes a problem in diabetes and the mechanisms that are involved are unknown. This project helped to shed light on the complex mechanisms that underlie diabetic neuropathy and pinpoint potential targets for future therapeutic intervention.

Relevant Publications

N/A

Career Aspirations

As a clinician and with a PhD, I intend to focus on two aspects of academia; teaching and research. As a passionate educator, I hope to be in a position to do both since these are vital for medical education and for the wholesome development of future health care professionals.