Nerve Injury Pain: It's All About Glutamate in Peripheral (not CNS) Neurons

Luc Dupont Jasmin MD, PhD, FRCS(C), FACS; Kerui Gong Ph.D.; Ling-Hsuan Kung Ph.D.; Peter Ohara; Aditi Bhargava Ph.D

Departments of Anatomy and Surgery, University of California San Francisco, San Francisco, CA 94143.

Introduction

Glutamate is the most common excitatory neurotransmitter in the nervous system and recognized to be involved in nociceptive processes in the CNS. There is increasing evidence that glutamate also plays a role in nociception in the peripheral nervous system but the processes have not been fully investigated. Here we present data showing that following nerve injury, neurons in the dorsal root ganglia change their response to glutamate application.

Methods

A standard chronic constriction nerve injury (CCI) was performed on the sciatic nerve of adult male Sprague Dawley rats. Seven days post nerve injury the rats were anesthetized and the L4 and L5 dorsal root ganglia (DRG) were removed, placed in a recording chamber, perfused with artificial CSF and patch clamp recordings performed on small diameter neurons (<30µm) using standard methods. Glutamate receptor agonists and antagonists were applied via a 30µm tip diameter pipette placed 100µm from the recorded neuron.

Results

Neurons from control DRG responded to application of NMDA, AMPA, KA and mGluR selective agonists with inward currents and the effects of the agonists were blocked by prior application of the selective antagonists (Fig. 1). Neurons from nerve injured ganglia had decreased action potential threshold and nerve injured neurons showed increased inward currents in response to application of selective agonists (Fig. 2). Because there is known to be interactions between the receptor subtypes, control ganglia were incubated in DHPG (mGluR agonist) for 2 hours prior to patch clamp recording. Under these conditions AMPA selective agonists resulted in decreased inward currents compared with controls (Fig. 3).

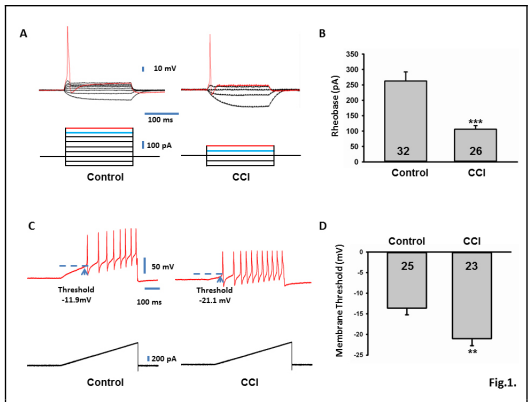

Fig. 1. After CCI of the sciatic nerve, DRG neurons show increased membrane excitability (reduced rheobase) and lowered action potential threshold.

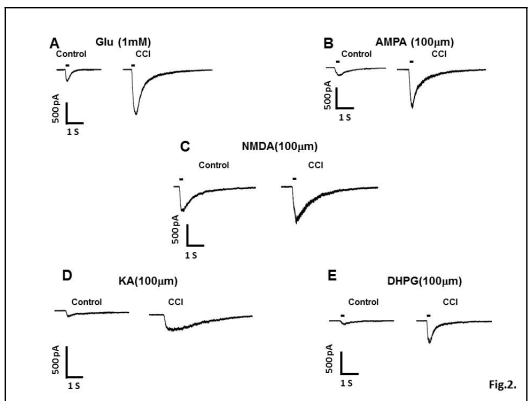

Fig. 2. Following CCI of the sciatic nerve, small diameter neurons show increased currents to selective glutamate receptor subtype agonists compared to non-injured controls.

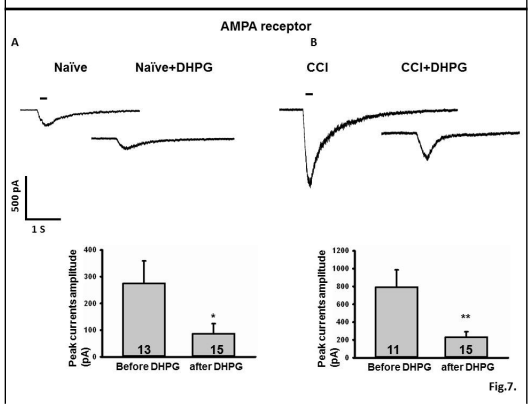

Fig. 3. Incubation of DRG with the Group 1 mGluR receptor agonist DHPG results in a reduction of inward currents induced by application of AMPA. Increased AMPA currents found after CCI of the sciatic nerve are reduced to near normal levels by DHPG incubation.

Conclusions

These results show that peripheral nerve injury results in increased excitability of small diameter neurons and also increases the response to glutamate. mGluR receptors appear to play a key role in after nerve injury by changing the response of ionotropic glutamate receptors by an as yet undetermined mechanism. These findings open new opportunities for treating neuropathic pain using glutamate acting drugs that act only in the periphery, therefore avoiding many CNS side effects of currently used therapies.

Learning Objectives

By the conclusion of this session, participants should be able to: 1) Describe the importance of glutamate receptors in peripheral nerve injury, 2) Understand the interaction between different classes of glutamate receptors in the peripheral nervous system. 3) Understand the importance peripheral nerves activation in generating and maintaining neuropathic pain.

References

Kung LH, Gong K, Adedoyin M, Ng J, Bhargava A, Ohara, P.T., Jasmin, L. (2013) Evidence for Glutamate as a Neuroglial Transmitter within Sensory Ganglia. PloS one 8: e68312.