Axotomy prevents capsaicin-induced sensory ganglion cell degeneration

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Abstract—A particular group of mammalian primary afferent neurons involved in nociception is characterized by its specific sensitivity to capsaicin, the pungent principle of red pepper. A striking manifestation of neuronal capsaicin sensitivity is the degeneration of a morphologically well characterized population of sensory ganglion cells following a systemic injection of this compound. The present study demonstrated that prior transection of the peripheral axons of these neurons protects them from the neurotoxic action of systemically administered capsaicin. It is suggested that this phenomenon is related to an impairment of axon transport mechanisms. It is concluded that maintenance of capsaicin sensitivity is critically dependent on the integrity of the peripheral branch of the primary sensory neuron and peripherally derived trophic factor(s) may profoundly influence the functional traits of sensory ganglion cells.

Keywords: Capsaicin; neurotoxicity; sensory ganglion; degeneration; axotomy; capsaicin sensitivity; axonal transport.

1. INTRODUCTION

Capsaicin-sensitive primary afferent neurons form a separate division of the sensory nervous system involved in nociception and in local regulatory functions of a variety of tissues and organs (Jancsó, 1968; Szolcsányi, 1984; Jancsó et al., 1987; Maggi and Meli, 1988; Holzer, 1991). Capsaicin sensitivity appears to be a common trait of mammalian primary afferent neurons (Pierau et al., 1986; Jancsó et al., 1987), a prominent manifestation of which is the degeneration of a morphologically well characterized population of sensory ganglion cells following a systemic injection of capsaicin (Jancsó et al., 1977, 1985; Ritter and Dinh, 1988; Hiura et al., 1992). A decrease in sensitivity with maturation of sensory ganglion cells to the neurotoxic action of capsaicin is well documented (Jancsó and Király, 1981; Hiura et al., 1992).

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Information on the factors which may determine or modulate the sensitivity of mature sensory neurons to the neurodegenerative action of capsaicin is limited. Previous studies concerned with the effects of capsaicin applied directly onto a peripheral nerve have led us to suppose that the maintenance of the structural integrity of the peripheral branch of the sensory ganglion cell may be crucial in keeping the selective vulnerability of the neuron to this neurotoxin. In fact, treatment of a peripheral nerve with capsaicin prior to a systemic administration of capsaicin resulted in a significant decrease in the proportion of degenerating nerve cells in the relating ganglia (Jancsó and Ambrus, 1994). Since nerve growth factor (NGF) has been shown to regulate neuronal capsaicin sensitivity \textit{in vitro} (Winter \textit{et al}., 1988; Aguayo and White, 1992), it has been suggested that by inhibition of axon transport processes (Gamse \textit{et al}., 1982), perineural application of capsaicin may have deprived the affected neurons of peripherally derived NGF resulting in a decreased sensitivity to the neurodegenerative effect of this compound (Jancsó and Ambrus, 1994). Hence, it was hypothesized that peripherally derived trophic factor(s) may play a significant role in the regulation of neuronal capsaicin sensitivity also \textit{in vivo}. However, application of capsaicin may render afferent axons/neurons insensitive to the actions of the drug upon subsequent administrations, a phenomenon known as capsaicin desensitization (Jancsó, 1968). Therefore, the aim of the present study was to explore the possible modulatory effect of peripheral nerve section compromising axonal transport on the neurodegenerative action of systemically administered capsaicin in the adult rat.

2. MATERIALS AND METHODS

The experiments were performed on adult male Wistar rats weighing 220–250 g. Rats were anaesthetized with pentobarbital (Nembutal; 40 mg/kg, i.p.) and both sciatic nerves were exposed in the thigh under aseptic conditions. The right nerve was ligated and a 5 mm long distal segment of the nerve removed. On the contralateral side the nerve was exposed but otherwise left intact. Either 1 or 4 days later the animals were anaesthetized again and given a single s.c. injection of capsaicin at a dose of 100 mg/kg. After 3–4 h the rats were perfused transcardially with 4% formalin and the fifth lumbar dorsal root ganglia (DRG), the neuronal population of which consists up to 85% of cell bodies giving rise to afferent fibres running within the sciatic nerve (Yip, 1984; Aldskogius \textit{et al}., 1988), were dissected out. Tissue samples were postfixed with osmium tetroxide, dehydrated in ascending series in ethanol and then embedded in Araldite. Serial sections of 4 \mu m in thickness were cut from each ganglion and stained with Methylene Blue. Percentages of degenerating neurons were determined by counting all neurons which exhibited a clear-cut nucleolus in sections taken at a regular interval of 80 \mu m throughout the ganglion. Size–frequency distribution histograms of normal and degenerating sensory neurons were generated by measuring their sizes by means of a light microscope equipped with a camera lucida and a digitizing tablet connected to a computerized system (Jancsó and Lawson, 1990; Jancsó and Ambrus, 1994).