Effects of ICI 128,436 on Animal Models of Neuropathy

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Excess activity of the aldose reductase pathway resulting in sorbitol accumulation has been implicated in the pathogenesis of diabetic complications. ICI 128,436 (3-(4-bromo-2-fluorobenzyl)-4-oxo-3 H-phthalazin-1-yl acetic acid) is a potent non-competitive inhibitor of aldose reductase. (IC₅₀ in vitro 2.6 × 10⁻⁸M). In STZ diabetic rats, ICI 128,436 reduces sciatic nerve sorbitol levels by 50% at a once daily oral dose of 3.1 mg/kg. Fructose levels are similarly reduced and myo-inositol depletion is prevented. Complete normalisation of nerve sorbitol is achieved at a dose of 20 mg/kg. Similar effects are seen in other tissues.

The effects of ICI 128,436 on a range of animal models of neuropathy have been investigated. ICI 128,436 treatment has been shown to

i) prevent the reduction in sciatic nerve conduction velocity.
ii) protect axonal transport of choline acetyl transferase in sciatic nerve and vagus.
iii) sustain tissue levels of choline acetyl transferase in the iris.
iv) modify the reduction in sensory threshold in short term diabetes.
v) protect vagal control of heart rate.

In conclusion, the aldose reductase pathway appears to play a fundamental role in the aetiology of diabetic neuropathy and ICI 128,436 treatment has a beneficial effect on both acute and chronic abnormalities.

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