

THE EFFECT OF ROFLUMILAST, A CLINICALLY AVAILABLE PHOSPHODIESTERASE-4 INHIBITOR, ON AXONAL REGENERATION IN A RAT MODEL OF PERIPHERAL NERVE INJURY

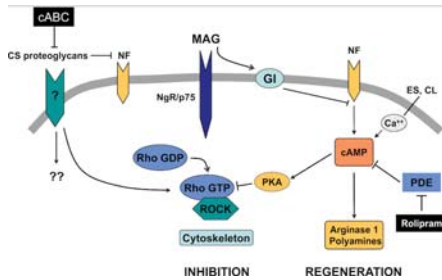
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OBJECTIVE

The debilitating nature of peripheral nerve injuries and the limited success of surgical repair make it important to explore pharmacological means to enhance nerve regeneration.

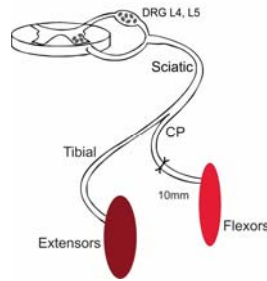
We have recently shown that rolipram, a phosphodiesterase-4 (PDE-4) inhibitor that elevates cAMP, promotes peripheral nerve regeneration and significantly increases the numbers of motor and sensory neurons that regenerated axons after nerve transection and repair in rats.¹ However, rolipram is only used for research purposes; it is not indicated for clinical use.



With the development of roflumilast, a PDE-4 inhibitor currently being used clinically for the treatment of chronic obstructive pulmonary disease, there is interest in investigating its potential role in human peripheral nerve regeneration.

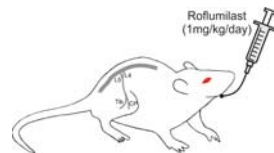
METHODS

Using aseptic technique and inhalation anesthesia, acutely axotomized common peroneal (CP) nerves were sutured to a freshly cut CP nerves in 20 male Wistar rats.



The animals were then treated daily for 14 days orally by gavage with either:

- roflumilast (dose 1.0mg/kg/day) or
- vehicle (Methocel suspension only)

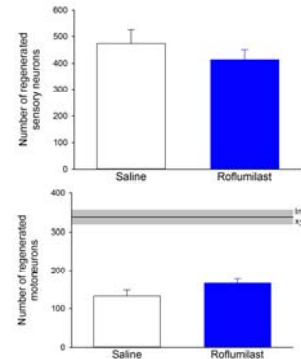


Fourteen days after nerve anastomosis, Fluororuby was applied to the distal stump of the CP nerve 10mm from the repair site for enumeration of motor and sensory neurons that regenerated their axons by dissection of the lumbosacral ventral nerve roots and dorsal root ganglia (DRG).

RESULTS

No significant difference was found in the peripheral nerve regeneration following axotomy and repair between the vehicle group and the roflumilast-treated group of rats.

The number of motoneurons that regenerated in rats treated with roflumilast was 132 +/- 16 (mean +/- standard error), compared to 167 +/- 11 treated with vehicle. The number of sensory neurons that regenerated after treatment with roflumilast was 414 +/- 38, compared to 474 +/- 53 with vehicle.

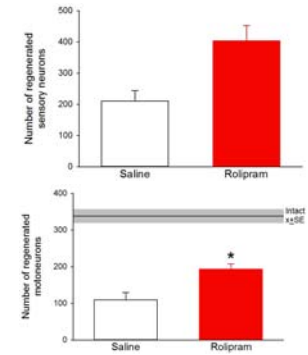


Neither the motoneurons nor the sensory neurons showed a significant difference in axon regeneration between the two groups using an independent t-test.

No toxicity was noted in the animals treated with roflumilast at a dose of 1.0mg/kg/day.

CONCLUSIONS

Given as a daily oral dose, roflumilast was ineffective. Perhaps more localized and more frequent administration of the drug would result in improved nerve regeneration. In previous studies showing the benefit of the PDE-4 inhibitor rolipram, the drug was delivered at a continuous rate over 7, 14, or 21 days through a subcutaneously implanted pump on the back of the rat.



Further study is needed to investigate the use of pharmacological means to enhance peripheral nerve regeneration, using a clinically available drug.

REFERENCES

1. Udina E, Ladak A, Furey M, Brushart T, Tyreman N, Gordon T. Rolipram-induced elevation of cAMP or chondroitinase ABC breakdown of inhibitory proteoglycans in the extracellular matrix promotes peripheral nerve regeneration. *Experimental Neurology* 223:143-52. 2010.