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THE GLP-1 ANALOGUE ROSE-010 AND GLP-1 SHARE THE SAME RECEPTOR MECHANISM FOR INHIBITION OF THE MIGRATING MYOELECTRIC COMPLEX IN THE CONSCIOUS RAT: STUDIES WITH EXENDIN(9-39)AMIDE

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Conclusion

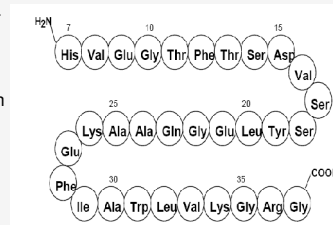
MMC inhibition following ROSE-010 IV is similar to that of GLP-1 IV and possible to inhibit by the same blocker, exendin(9-39)amide.

This indicates that one and the same receptor mechanism is operative for the inhibitory action of these two ligands, ROSE-010 and GLP-1.

Background

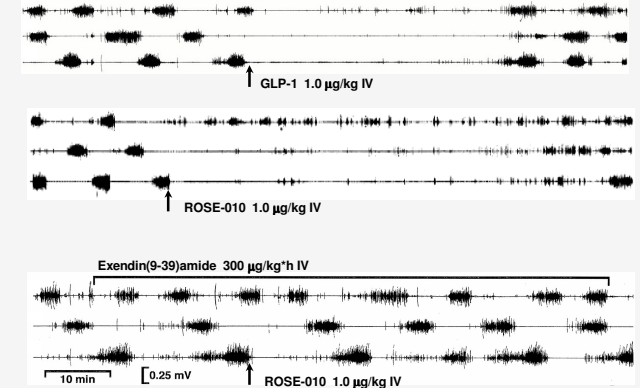
ROSE-010 is a 31 amino acid GLP-1 (7-37) analogue with Ala substituted by Val in position 8. ROSE-010 given by the subcutaneous route reduces bowel spasm and relieves acute pain attacks in patients with IBS.

We have compared the effects of ROSE-010 with those of native GLP-1 and extended our studies to involve an exendin receptor blocker, exendin(9-39) amide, known to specifically bind to the receptor for GLP-1.



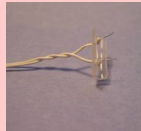
Results

ROSE-010 at all doses had a prompt inhibitory effect on the MMC, similar to GLP-1 in all animals. This motility effect was prevented by exendin(9-39)amide.



Methods

Male Sprague-Dawley rats (250-300 g) were used. Bipolar electrodes were implanted on the serosa of the small intestine 5 (D), 15 (J1), 25 (J2) cm from the pyloric sphincter and tunnelled subcutaneously to exit at the neck



A catheter was placed in the jugular vein for drug administration; this exited also at the back of neck. One week after surgery the studies commenced.



Fasting motility was recorded for a control period of 60 min with 4 MMCs.

Then, the following treatments were given IV with continuous recording of intestinal myoelectric activity.

Groups 1, 2, 3: ROSE-010 1.0, 10 and 100 µg/kg (n=10)

Groups 4, 5, 6: GLP-1 1.0, 10 and 100 µg/kg (n=10)

Groups 7, 8, 9: ROSE-010 1.0, 10 and 100 µg/kg + Exendin(9-39)amide 300 µg/kg/h infusion (n=6)

Groups 10, 11, 12: GLP-1 1.0, 10 and 100 µg/kg + Exendin(9-39)amide 300 µg/kg/h infusion (n=6)

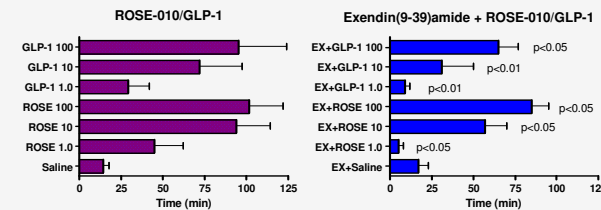


Aim

To compare ROSE-010 with GLP-1 in the MMC model when administered by the IV route, with or without exendin(9-39)amide as receptor blocker.

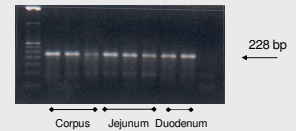
Results

Comparison of the inhibitory effect of GLP-1 and ROSE-010 with and without exendin(9-39)amide



Discussion

A PCR product of the GLP-1/exendin receptor has been found in the GI tract of the rat.



We will investigate the action mechanism of ROSE-010 in order to clarify the GI muscle-relaxing and pain-relieving effect of this GLP-1 analogue in IBS pain attacks.

