

PEPTIDE-DERIVATIZED NANOPARTICLES AS CARRIERS OF DRUGS INTO THE CENTRAL NERVOUS SYSTEM

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Several brain diseases are difficult to treat owing to the presence of the blood brain barrier (BBB) that prevents the passage of many drugs, and to the glycoprotein P efflux system (PgpES) that is largely expressed in the brain capillary endothelial cells and that is responsible for the rapid efflux of xenobiotics. A promising approach to this problem seems to be the loading of drugs into polymeric nanoparticles (Np) that possess a higher stability than other colloidal carriers, such as liposomes, and that cross the BBB. In the present research we studied the ability of Np made of Poly (D,L-lactide-co-glycolide) (PLGA) conjugated with the glycosilated heptapeptide Gly-L-Phe-D-Tyr-Gly-L-Phe-L-Leu-L-Ser(O-β-D-Glucose)CONH₂ (g7) (g7-Np) to cross the BBB and to carry into the brain a drug that cannot penetrate the CNS because substrate of PgpES, i.e. the opiate loperamide. *Methods.* Adult Wistar rats were i.v. injected with g7-Np loaded with loperamide at the doses of 1.8 or 2.7 mg/kg; control rats received g7-Np not loaded with loperamide, or a hydroalcoholic loperamide solution (2.7 mg/kg), or buffer solution, or a suspension of unloaded g7-Np in a solution of loperamide (2.7 mg/kg). Another group was treated with Np made of PLGA not conjugated with g7 (B-Np), loaded with loperamide (2.7 mg/kg). Pain threshold was measured by the hot plate test (52±0.2°C) 15, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, 360, 390 and 420 min after treatment. *Results.* A dose-related antinociceptive effect was observed only in rats treated with the loperamide-loaded g7-Np, with a 25-30% MPE at 30-60 min, a maximum response (45-60% MPE) at 240 min, and a still significant effect at 360-420 min. Naloxone (0.1 mg/kg), injected at the time of maximum effect (245 min) completely and promptly abolished the antinociceptive response. On the other hand, no significant antinociceptive effect was observed in rats treated with loperamide-loaded (2.7 mg/kg) B-Np. *Conclusions.* Our present results show that polymeric nanoparticles made of glycopeptide-derivatized PLGA are effective carriers of drugs through the BBB, and may represent a novel approach to the pharmacological treatment of severe, often incurable, CNS diseases, such as tumors. They might also make possible the therapeutic use of molecules, such as many neuropeptides, endowed with very important effects at the CNS level (anorexant, penile erection-inducing, anti-shock, brain and heart protection from ischemic damage, in the case of several melanocortins; anorexant and sexual stimulating effects, in the case of oxytocin; etc.).