P30 Brain uptake through the blood-brain barrier, pharmacokinetics and analgesic effect of [^{3}H]Oxytocin in the rat

Ji-Hyun Park, Young-Sook Kang

College of Pharmacy, Sookmyung Womens' University, Seoul 140-742, Korea

Oxytocin(OT) is a neurohypophyseal nonapeptide which plays an important role in CNS function as well as uterine contraction during delivery. Furthermore, recently it has been reported that OT may also have analgesic effect and found that the release of OT is related with opioid receptors, especially κ and μ.

To establish the safty of OT as analgesics used for pregnant wemen, [^{3}H]OT was used to get pharmacokinetics parameters and to quntitate blood brain barrier(BBB) permeability by intraveneous injection technique or internal carotid artery perfusion/capillary depletion method(ICAP/DPM). With intraveneous injection, the BBB permeability surface(PS) area products at 60min for [^{3}H]OT and [^{14}C]sucrose, vascular space marker, were 3.82 $\pm$ 0.57 $\mu\ell$/min/g and 0.38 $\pm$ 0.08 $\mu\ell$ min/g, respectively. The value of [^{14}C]sucrose was coincident with that of an existing report (0.39 $\pm$ 0.05 $\mu\ell$/min/g). This level for OT was manyfold lower than we expected. we suggested that OT is metabolically unstable and corrected plasma conentration with intact OT in plasma by HPLC analysis. Consequently, area under plasma concentration curve (AUC) decreased to less 20% and total plasma clearance (Clt) increased five times. Thus we can not compare net BBB PS product by intravenous injection with that obtained by the ICAP/CDM, due to its fast metabolism in blood. The brain distridution

volume (V_D) for [^{3}H]OT and [^{14}C]sucrose estimated with the ICAP/CDM was similar.

Analgesic effect of OT injected through a jugular vein on nociception was evaluated by tail-flick method. Base-line latencies were recorded 30 min and 15 min before the i.v. injection. The cutoff time was set to 10 sec. Antinociceptive effects of OT injected in a dose of 0.2 mg/kg or 2 mg/kg showed dose-dependence and reduction in proportion of its plasma concentration. Thus these represent that OT may be short acting analgesics owing to its fast metabolism in plasma.

From the results, we elucidated permeability of OT through the BBB is very small and the fact that OT administered jugularly also has a short acting analgesic effect. However, a high dose of OT should be used to gain analgesic effects when administered systemically so that we cannot avoid the unexpected fucntions of OT on systemic compartment, especially the cardiovascular system. Thus to understand more on CNS function of OT as analgesics and to establish the safety by using a lower dose, invulnerable delivery method to brain should be developed.