**Loperamide Interacts with Uptake Transporters of the OATP Family**

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**Background/Introduction:** Uptake and efflux transporters play an important role in drug absorption, distribution and elimination. Some opioids like loperamide, morphine and methadone are known substrates of the efflux transporter p-glycoprotein, which limits brain penetration. However, the interaction of opioid drugs with uptake transporters has not been sufficiently investigated so far. Therefore, we investigated the influence of loperamide on multispecific uptake transporters of the organic anion transporting polypeptide (OATP) family.

**Methods:** HEK 293 cells were stably transfected with OATP1A2, OATP1B1, OATP1B3, OATP2B1 or the empty vector as control. Inhibitory effects of increasing loperamide concentrations were studied in competition assays (n = 9) using established, radiolabelled reference substrates. Intracellular accumulation of estrone-3-sulfate (OATP1A2) and bromosulfophthalein (OATP1B1, OATP1B3, OATP2B1) was measured by liquid scintillation counting after cell lysis. Furthermore, cellular uptake of radiolabelled loperamide into OATP2B1 cells was assessed (n = 9).

**Results:** Loperamide potently inhibited all investigated OATPs (OATP1A2, OATP1B1, OATP1B3: IC50: 0.3 – 3 µM; OATP2B1: IC50 = 103 µM) and was a substrate of OATP2B1 (Km = 3 µM, vmax = 48 pmol/mg\*min).

**Conclusion:** In this *in vitro* study loperamide was a potent, non-selective inhibitor of various OATPs. Therefore, loperamide might cause interactions with other OATP substrates such as statins. Furthermore, cellular uptake of loperamide was mediated by OATP2B1, which is ubiquitously expressed at important absorption barriers (e.g. intestinal epithelium and blood brain barrier) and at elimination sites (e.g. hepatocytes). However, loperamide uptake by OATP1A2, OATP1B1 and OATP1B3 has yet to be evaluated. Furthermore, these findings suggest that other opioids might as well interact with OATPs and this needs to be further investigated.