OATP1A2 and OATP2B1 Are Interacting with Dopamine-Receptor Agonists and Antagonists.

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Interaction with the dopaminergic system in the central nervous system is either therapeutically intended or it is a side effect. In both cases, dopamine-receptor agonists (DRA) like the ergoline derivative bromocriptine and dopamine-receptor antagonists (DRAn) like metoclopramide have to cross the blood-brain barrier (BBB). The organic anion transporting polypeptides (OATP) 1A2 and 2B1 are cellular uptake carriers for a variety of endogenous and xenobiotic compounds. As both transporters are expressed in endothelial cells of the BBB, the aim of the present study was to determine whether the DRA bromocriptine, cabergoline, and pergolide and the DRAn metoclopramide and domperidone are interacting with OATP1A2 and 2B1 and could therefore be candidate genes modifying wanted and unwanted effects of these drugs. Localization of both transporters in the brain was confirmed using LC-MS/MS and immunofluorescence stainings. For the functional studies, MDCKII cells stably expressing OATP1A2 or 2B1 were used. Initial interaction studies with the well-characterized transporter substrate estrone 3-sulfate revealed that all tested compounds except pergolide inhibit the transport function of both proteins with the most potent effect for bromocriptine (IC; 50; = 2.2 μM (OATP1A2) and IC; 50; = 2.5 μM (OATP2B1)). Further studies using the indirect competitive counterflow method identified bromocriptine, cabergoline, and domperidone as substrates of both transporters, whereas metoclopramide was only transported by OATP1A2. These findings were verified for domperidone by direct measurements using its tritium-labeled form as a tracer. Moreover, the transporter-mediated uptake of this compound was sensitive to the OATP1A2 and OATP2B1 inhibitor naringin. In conclusion, this study suggests that OATP1A2 and 2B1 may play a role in the uptake of DR agonists and antagonists into the brain.

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