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OAT4/SLC22A11-MEDIATED UPTAKE OF 16α-HYDROXY DEHYDRO EPIANDROSTERONE SULFATE AT THE PLACENTAL BARRIER

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ABSTRACT

Estriol is a major estrogen produced during pregnancy and is synthesized from the fetal precursor 16α-hydroxy dehydroepiandrosterone sulfate (16α-OH DHEAS) in the syncytiotrophoblast constituting the placental barrier. Organic anion transporter(s) at the basolateral membrane of the syncytiotrophoblast is pivotal in the uptake of 16α-OH DHEAS from the fetus and would also influence the fetal concentration of some drugs. The purpose of this study is to clarify the transport mechanism of 16α-OH DHEAS at the placental barrier. [^{3}H]16α-OH DHEAS was enzymatically converted from [^{3}H]DHEAS using recombinant human CYP3A7. The uptake of [^{3}H]16α-OH DHEAS at the placental barrier was characterized using forskolin-induced differentiated JEG-3 human choriocarcinoma cells. The uptake of [^{3}H]16α-OH DHEAS via human organic anion transporter 4 (OAT4/SLC22A11) and organic anion transporter polypeptide 2B1 (OATP2B1/SLCO2B1) were examined using OAT4- or OATP2B1-transfected COS7 cells. The uptake of [^{3}H]16α-OH DHEAS in differentiated JEG-3 cells was significantly inhibited by 1 mM DHEAS, estrone sulfate (E_1S), and bromosulfophthalein (BSP), but not by 1 mM tetraethylammonium (TEA). Human OAT4-transfected COS7 cells exhibited [^{3}H]16α-OH DHEAS uptake activity with a K_m of 7.4 μM, and moreover, this uptake was also inhibited by DHEAS, E_1S, and BSP, but not by TEA. On the other hand, the OATP2B1-mediated uptake of [^{3}H]16α-OH DHEAS was not exhibited. In conclusion, OAT4 appears to play a predominant role in the uptake of [^{3}H]16α-OH DHEAS from the fetal circulation and contribute to the estriol synthesis during pregnancy.

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