

## A37

### **A relationship between membrane permeability of amphetamines and serotonin efflux via serotonin transporters**

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#### **Background**

It has been noticed by our group [1] that p-chloroamphetamine (PCA)-induced SERT current “deactivates” slower upon removal of PCA from the external solution, when compared to the deactivation of serotonin (5-HT)-induced current. This was observed in stably transfected human embryonic kidney (HEK) cells as well as in *Xenopus laevis* oocytes injected with hSERT-RNA, for PCA/5-HT concentrations between 1 and 30  $\mu\text{M}$ . Following the removal of higher concentrations of PCA ( $>30 \mu\text{M}$ ) from the bath solution we witnessed an intriguing, but yet paradoxical current rise.

#### **Methods and results**

Here we try to explain both findings with a model in which due to PCA leakage from the interior of the cell, SERT activity is prolonged. The increase of current following removal of high PCA concentrations is thus a consequence of the combination of “PCA leakage” and a bell-shaped dose-response relationship for the activation of the substrate-induced current. We then explored the relevancy of these findings for PCA-induced [ $^3\text{H}$ ]5-HT release employing superfusion experiments. Analogous to the described slow deactivation of the substrate-induced current, also a slow deactivation of 5-HT release upon washout of PCA was found.

#### **Conclusions**

This strongly supports the notion that leakage of amphetamines from the lumen of the cell is crucially implicated in amphetamine action. PCA leaking from the interior of the cell can reactivate SERT and thus increase the probability of the occurrence of outward transport. Here we propose that amphetamines can cause 5-HT efflux due to their ability to cycle (passive leak through the membrane and active reuptake through SERT), an ability that is not shared by the endogenous substrate 5-HT.

#### **Reference**

1. Seidel S, Singer EA, Just H, Farhan H, Scholze P, Kudlacek O, Holy M, Koppatz K, Krivanek P, Freissmuth M, Sitte HH: **Amphetamines take two to tango: an oligomer-based counter-transport model of neurotransmitter transport explores the amphetamine action.** *Mol Pharmacol* 2005, **67**:140–151.