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MEETING ABSTRACT

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Kinetic interrogation of substrate binding and transport in the serotonin transporter

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Background: The serotonin transporter (SERT) controls serotonin signaling by reuptake of serotonin from the extracellular space. Moreover, SERT (together with the other monoamine transporters) is a prominent target of a variety of psychoactive drugs, ranging from illicit to therapeutic substances. Some of these drugs are inhibitors, whereas others are substrates. These substances, and their action on SERT, have been the subject of intense study [1]. However, kinetic knowledge on the mechanism by which SERT orchestrates substrate binding and translocation has been lacking because of technical limitations.

Methods: We thus utilized the high temporal resolution of the whole-cell patch-clamp technique [2,3] to unravel the kinetic determinants of serotonin transporter substrate selectivity and substrate transport. Moreover, we developed a refined kinetic model of SERT function that accounts for the experimental data.

Results: We show that our approach is suitable to measure substrate-binding kinetics without the need of any radioligands as surrogate, and with a temporal resolution that is not achievable by conventional biochemical methods.

Discussion: Our findings may foster attempts of rational drug design by adding kinetic knowledge to available structural data.

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