SIMPOSIO / SYMPOSIA 8

Coordinador Dr. Gonzalo E. Torres (LUC), "New Insights into Monoamine Transporter Function: From Structure to Disease". Expositores: Angelica Fierro (PUC), José Pino (U. Atacama), Aurelio Galli (U. Alabama), Gonzalo Torres, (U. New York).

MECANISMOS DE LOS TRANSPORTADORES DE MONOAMINA: REVELACIONES DESDE MODELAMIENTO MOLECULAR. MONOAMINE TRANSPORTER MECHANISMS: INSIGHTS FROM MOLECULAR MODELING.

Neurotransmitter transporters (NTTs) are 12-transmembrane domain proteins which are involved in the regulation of neurotransmitter (NT) levels. Using ion gradients, NTTs moves the neurotransmitters from outside to inside surfaces of the cell membrane regulating the monoamine concentrations which are relevant to several biological functions. Because of that, NTTs have been widely explored as biological target of compounds as recreational drugs, antidepressants and antipsychotics, among others. Here we evaluate SERT interacting with phenethylamine derivatives and serotonin in order to generate new structural insights related with the translocation mechanism. Thus, describing specific interactions inside the transporter, stabilization and free energy of each complex using molecular docking, molecular dynamic simulation (1.5 microseconds) and Molecular Mechanics Poisson-Boltzmann Surface Area (MM/PBSA) calculations was possible to characterize each system. Our results provide additional structural insights into the mechanism by which substrates are translocated.

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INTERACCIÓN ENTRE HORMONAS, ENDOCANABINOIDES Y EL TRANSPORTADOR DE DOPAMINA EN LAS ACCIONES DE LA COCAÍNA. INTERPLAY BETWEEN HORMONES, ENDOCANNABINOIDS, AND THE DOPAMINE TRANSPORTER IN THE ACTIONS OF COCAINE.

Agonism of the glucagon-like peptide 1 (GLP-1) receptor (GLP-1R) has been effective at treating aspects of addictive behavior for a number of abused substances, including cocaine. However, the molecular mechanisms and brain circuits underlying the therapeutic effects of GLP-1R signaling on cocaine actions remain elusive. Recent evidence has revealed that endogenous signaling at the GLP-1R within the forebrain lateral septum (LS) acts to reduce cocaine-induced locomotion and cocaine conditioned place preference, both considered dopamine (DA)-associated behaviors. DA terminals project from the ventral tegmental area to the LS and express the DA transporter (DAT). Cocaine acts by altering DA bioavailability by targeting the DAT. Therefore, GLP-1R signaling might exert effects on DAT to account for its regulation of cocaine-induced behaviors. We show that the GLP-1R is highly expressed within the LS. GLP-1, in LS slices, significantly enhances DAT surface expression and DAT function. Exenatide (Ex-4), a long-lasting synthetic analog of GLP-1 abolished cocaine-induced elevation of DA. Interestingly, acute administration of Ex-4 reduces septal expression of the retrograde messenger 2-arachidonylglycerol (2-AG), as well as a product of its presynaptic degradation, arachidonic acid (AA). Notably, AA reduces septal DAT function pointing to AA as a novel regulator of central DA homeostasis. We further show that AA oxidation product γ-ketoaldehyde (γ-KA) forms adducts with the DAT and reduces DAT plasma membrane expression and function. These results support a mechanism in which postsynaptic septal GLP-1R activation regulates 2-AG levels to alter presynaptic DA homeostasis and cocaine actions through AA.

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WATCH FLIES TEACHING US MECHANISMS OF NEUROLOGICAL DISORDERS

Parkinson's disease (PD) is a neurodegenerative disorder affecting over 6.1 million people worldwide. Studies of highly-penetrant mutations identified in early-onset familial parkinsonism have contributed to our understanding of the mechanisms underlying PD. Dopamine (DA) transporter (DAT) deficiency syndrome (DTDS) is a type of infantile parkinsonism-dystonia that shares clinical features with PD. Here, we define structural, functional, and behavioral consequences of a Cys substitution at R445 in human DAT (hDAT R445C), identified in a patient with DTDS. This R445 substitution disrupts a phylogenetically conserved intracellular (IC) network of interactions that compromise the hDAT IC gate. The disruption of this IC network supported a channel-like intermediate of hDAT and compromised hDAT function. Drosophila melanogaster expressing hDAT R445C show impaired hDAT activity, DA dysfunction in isolated brains and abnormal motor behaviors monitored at high-speed time resolution. These behaviors are linked with altered dopaminergic signaling, loss of DA neurons and decreased DA availability.

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EL TRANSPORTE REVERSO DE MONOAMINAS: CUAL ES EL SIGNIFICADO FISIOLOGICO?. THE REVERSE TRANSPORT OF MONOAMINES: WHAT IS THE PHYSIOLOGICAL SIGNIFICANCE?.

Monoamine transporters (MATs) play a crucial role in the reuptake of monoamines, terminating the action of these neurotransmitters and recycling them back to the presynaptic terminal. Different drugs approved for the treatment of neuropsychiatric disorders (depression, anxiety, attentional disorders, among others) interact with MATs, blocking the reuptake and increasing the extracellular concentration of monoamines. In addition, some of these compounds interact with MATs to induce transmitter efflux through the transporter. Monoamine transporters are highly regulated through signaling mechanisms and protein-protein interactions. We have recently discovered a new interaction between the dopamine transporter (DAT) and Gβγ subunits of G proteins. Our data indicate that the binding of Gβγ to the carboxy terminus of DAT promotes DA efflux. In this presentation, I will discuss whether the related serotonin and norepinephrine transporters (SERT and NET, respectively) present a similar Gβγ regulation. The physiological consequences of these novel interactions will also be discussed.

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