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Multiple functions of neuronal plasma membrane neurotransmitter transporters

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ABSTRACT

Removal from receptors of neurotransmitters just released into synapses is one of the major steps in neurotransmission. Transporters situated on the plasma membrane of nerve endings and glial cells perform the process of neurotransmitter (re)uptake. Because the density of transporters in the membranes can fluctuate, transporters can determine the transmitter concentrations at receptors, thus modulating indirectly the excitability of neighboring neurons. Evidence is accumulating that neurotransmitter transporters can exhibit multiple functions. Being bidirectional, neurotransmitter transporters can mediate transmitter release by working in reverse, most often under pathological conditions that cause ionic gradient dysregulations. Some transporters reverse to release transmitters, like dopamine or serotonin, when activated by 'indirectly acting' substrates, like the amphetamines. Some transporters exhibit as one major function the ability to capture transmitters into nerve terminals that perform insufficient synthesis. Transporter activation can generate conductances that regulate directly neuronal excitability. Synaptic and non-synaptic transporters play different roles. Cytosolic Na^+ elevations accompanying transport can interact with plasmalemmal or/and mitochondrial Na^+/Ca^{2+} exchangers thus generating calcium signals. Finally, neurotransmitter transporters can behave as receptors mediating releasing stimuli able to cause transmitter efflux through multiple mechanisms. Neurotransmitter transporters are therefore likely to play hitherto unknown roles in multiple therapeutic treatments.

Contents

Abbreviations: 4-AP, 4-aminopyridine; AC, anion channels; CGP37157, 7-chloro-5-(2-chlorophenyl)-1,5-dihydro-4,1-benzothiazepin-2(3*H*)-one; CICR, Ca^{2+}-induced Ca^{2+} release; DA, dopamine; DAT, dopamine transporter; EAAT, excitatory amino acid transporter; GABA, γ-aminobutyric acid; $GABA_A$ receptor, GABA receptor type A; GAD, glutamic acid decarboxylase; GAT1, GABA transporter 1; GlyT1, glycine transporter 1; GlyT2, glycine transporter 2; $InsP_3$, inositoltrisphosphate; KB-R7943, 2-[2-[4-(4-nitrobenzyloxy)phenyl] ethyl]isothiurea; mNCX, mitochondrial Na^+/Ca^{2+} exchanger; NCX, Na^+/Ca^{2+} exchanger; NFPS, N-[(3R)-3-([1,1′-biphenyl]-4-yloxy)-3-(4-fluorophenyl)propyl]-*N*-methylglycine hydrochloride; NMDA receptor*N*-methyl-D-aspartate, receptor; NPPB, 5-nitro-2-(3-phenylpropylamino)-benzoic acid; PMCA, plasma membrane Ca^{2+}-ATPase; pNCX, plasmalemmal Na^+/Ca^{2+} exchanger; SERT, serotonin transporter; SNc, substantia nigra pars compacta; SOC, store operated channels; SPNs, striatal projection neurons; TRPC, transient receptor potential; vGAT, vesicular GABA transporter; vMAT, vesicular amine transporter; VSCCs, voltage-sensitive calcium channels; VTA, ventral tegmental area.

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1. Introduction

Transporters are integral membrane solute carrier proteins that selectively bind endogenous substrates at one side of the membrane and transfer them to the opposite side. A number of neurotransmitters, including dopamine, norepinephrine, serotonin, GABA and glutamate, are substrates for selective transporters which are mostly situated on the plasma membrane of nerve endings. Plasmalemmal neurotransmitter transporters have been the object of several review articles, more than ten entirely dedicated to these proteins published in the last few years (Sitte and Freissmuth, 2010; Kristensen et al., 2011; Schousboe et al., 2011; Blakely and Edwards, 2012; Bröer and Gether, 2012; Focke et al., 2013; Pramod et al., 2013; Zhou and Danbolt, 2013; Grewer et al., 2014; Rudnick et al., 2014; Jensen et al., 2015). There is increasing evidence that neurotransmitter transporters are multitasking devices able to perform different functions under physiological, pathological and pharmacological conditions. The first function attributed to neurotransmitter transporters is reuptake into nerve terminals of the transmitters just released in the synapse. A second function consists in the ability of transporters to bind transmitters present in the cytosol and to export them extracellularly by transporter reversal. Besides uptake and carrier-mediated release, there exist functions of neurotransmitter transporters that have been so far scarcely considered. These functions consist in mediating a variety of effects dependent on ionic fluxes and currents generated by the transporters as well as on interactions of transporters with targets coexisting on the same membrane, including different neurotransmitter transporters and presynaptic receptors. These additional functions of neurotransmitter transporters are the major object of the present review article.

2. Functions essentially consisting in transport of substrates across plasma membranes

The primary function of neuronal neurotransmitter transporters is to recognize the natural substrates present in the extracellular milieu and to transfer them into the cytosol of nerve endings. Neurotransmitters can sometimes be transported in the inside-out direction. Moreover, neurotransmitter transporters can be directly targeted by ligands structurally similar to the endogenous substrates, some of which are important drugs.

2.1. Neurotransmitter uptake

Neurotransmitter transporters have been attributed for long time only one physiological function: reuptake of the transmitters just released from nerve ending into the synapse, in order to terminate activation of postsynaptic receptors and prevent excessive receptor stimulation. Depending on the concentrations of substrates that need to be removed from the extracellular medium, the density of plasmalemmal transporters can fluctuate as these proteins can undergo trafficking between the plasma membrane and intraterminal storage vesicles. More precisely, it has become clear that the process of uptake can be modulated by transporters which can determine the concentrations of the neurotransmitters at receptors, thus regulating *indirectly* the excitability of neighboring cells. In addition, several proteins have been identified that interact with transporters in modes that influence the targeting of the transporters to specific membrane domains, the coupling of signaling pathways to transporter regulation and the intrinsic activity of the transporters (see, for reviews, Robinson, 2002, 2006; Gonzalez and Robinson, 2004; Steiner et al., 2008; Robertson et al., 2009; Kristensen et al., 2011; Blakely and Edwards, 2012). The mechanisms of action of important drugs like antidepressants are based on their ability to block the reuptake of biogenic amines by selective plasma membrane transporters. Relevant contribution to the removal of extracellular transmitters, particularly of the amino acid neurotransmitters GABA, glutamate and glycine, can be provided by astrocytic glial cells. Detailed information on various aspects of transmitter uptake can be found in the abundant literature available on the topic.

2.2. Neurotransmitter release by transporter reversal

Neurotransmitter transporters, as other transporters, are bidirectional and can, under some conditions, work in the inside-out direction, by a mechanism termed carrier-mediated release or