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Review

# The dopamine transporter: role in neurotoxicity and human disease

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**Abstract**

The dopamine transporter (DAT) is a plasma membrane transport protein expressed exclusively within a small subset of CNS neurons. It plays a crucial role in controlling dopamine-mediated neurotransmission and a number of associated behaviors. This review focuses on recent data elucidating the role of the dopamine transporter in neurotoxicity and a number of CNS disorders, including Parkinson disease, drug abuse, and attention deficit hyperactivity disorder (ADHD).


*Keywords:* Dopamine transporter; Neurotoxicity; Human disease

**Contents**



The neurotransmitter dopamine (DA) exerts important effects on locomotor activity, motivation and reward, and cognition (Bannon, 2004). The DA transporter (DAT) is a plasma membrane protein expressed exclusively in DA-synthesizing neurons. It clears dopamine released into the extracellular space, thereby regulating the amplitude and duration of DA signaling (for recent reviews, see Bannon et al., 2001; Mortensen and Amara, 2003; Uhl, 2003). In this overview, the physiological properties and regulation of the DAT are reviewed briefly, followed by a more detailed discussion of the specific role of the DAT in mediating neurotoxicity and its involvement in Parkinson disease, drug abuse, and attention deficit hyperactivity disorder (ADHD).

## Physiological properties of the DAT

Although specific DA uptake and accumulation in CNS nerve terminals were first described 35 years ago (see Iversen, 1971), it was the development of radiolabeled ligands with some specificity for the DAT (in the early

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1980s) and the cloning of DAT cDNAs and genes (in the early 1990s) that laid the foundation for our current understanding of DAT function and regulation. The DAT belongs to a family of $Na^+$- and $Cl^-$-dependent neurotransmitter transporters that also includes the norepinephrine, serotonin, GABA, glycine, proline, and taurine transporters. The DAT substrate DA is transported inwardly against its concentration gradient using the driving force of the sodium gradient across the plasma membrane. The stoichiometry of DA transport is generally thought to involve one DA molecule, two sodium ions, and one chloride ion, making the process potentially electrogenic. Recent electrophysiological studies, however, have revealed a previously unanticipated, complex pattern of DAT-mediated conductances not stoichiometrically linked to substrate movement (see Mortensen and Amara, 2003). In addition to a transport current elicited by DA and other substrates, a small depolarizing chloride conductance uncoupled to transport may modulate DA cell excitability. Furthermore, the DAT can transport DA in the reverse direction (i.e., into the extracellular space) under some circumstances, such as following exposure to amphetamines (see below). Thus, although the predominant action of the DAT is the termination of DA neurotransmission by recapture of extracellular DA, its physiological effects at any given time are the sum of inward and outward transport of substrate, as well as transport-dependent current and transport-independent channel-like properties.

## DAT expression and protein–protein interactions

The DAT gene is robustly expressed in midbrain DA neurons but few other cells. This extraordinary specificity of expression has been attributed to the combinatorial regulation of DAT gene expression by multiple positive and negative regulatory elements (see Bannon et al., 2001; Greenwood and Kelsoe, 2003). Within DA neurons, the DAT protein is robustly expressed in dendrites and soma (where it can mediate non-exocytotic DA release and modulate DA cell activity through its channel-like properties), and axonal extrasynaptic plasma membrane (with apparent exclusion from active synaptic zones) (Nirenberg et al., 1996, 1997).

Primary sequence and hydrophobicity analyses as well as a variety of experimental data strongly suggest that the DAT protein (620 amino acids in human) is composed of 12 membrane-spanning domains with intracellular N- and C-termini and multiple extracellular N-linked glycosylation sites. The DAT can exist as a phosphoprotein, with phosphorylated residues occurring primarily within the N-terminus (Granas et al., 2003; Lin et al., 2003). Although protein kinase C and other protein kinases can modulate DAT activity and trafficking/internalization, many of these effects may be indirect in nature and not mediated by direct phosphorylation of the DAT (see Mortensen and Amara, 2003). Recent data suggest that DAT oligomers (dimers or possibly tetramers) form within the endoplasmic reticulum as a prerequisite for proper trafficking to the plasma membrane (Sitte et al., 2004).

Several different proteins have been shown to interact with DAT, including PICK1 and Hic-5, which seem to affect the stability of the DAT at the plasma membrane (Carneiro et al., 2002; Torres et al., 2001). It is of significant interest that the abundant presynaptic protein α-synuclein also interacts with the DAT (Lee et al., 2001). Changes in the primary sequence or expression level of α-synuclein cause rare, heritable forms of Parkinson's disease (PD) in man and animal models, and even normal expression of α-synuclein may be involved in the generation of reactive oxygen species and induction of apoptosis in DA neurons (Eriksen et al., 2003; Maries et al., 2003). Although α-synuclein–DAT interaction has been demonstrated, the precise effects of α-synuclein on DAT clustering and functional activity are in dispute, likely as a result of differences in the cell culture methods utilized (Lee et al., 2001; Sidhu et al., 2004; Wersinger and Sidhu, 2003; Wersinger et al., 2003). In any case, α-synuclein's interaction with DAT provides one of several possible links between DAT and PD (see below).

## DAT-mediated neurotoxicity

In the early 1980s, self-administration of an illicitly synthesized meperidine analog resulted in the accidental exposure of numerous drug abusers to a toxic synthetic side product that caused severe parkinsonism (Langston et al., 1983). It was determined that a profound and selective loss of DA neurons in these subjects resulted from DAT-mediated accumulation of that compound's active metabolite, 1-methyl-4-phenyl-pyridinium ion ($MPP^+$), an inhibitor of mitochondrial complex I. $MPP^+$ administration to animals has provided an invaluable model for mechanistic and therapeutic studies of PD. Overexpression of DAT in transgenic mice results in a more profound $MPP^+$-mediated loss of DA cells; conversely, DAT knockout mice are highly resistant to $MPP^+$ neurotoxicity (Donovan et al., 1999; Gainetdinov et al., 1997). Exposure to the insecticide heptachlor reportedly increases murine DAT expression (Miller et al., 1999). These findings raise the possibility that exposure to $MPP^+$-like DAT-binding toxins (environmental or endogenous), perhaps in combination with individual variations in the levels of DAT expression, may play a contributory role in some cases of idiopathic PD.

## DAT and Parkinson's disease

Consistent with a possible role of the DAT in neurotoxin transport and the pathophysiology of idiopathic PD, the