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What can be learned from studies of multisubstrate mechanisms of neuronal dopamine transport?

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Abstract

The dopamine transporter (DAT) is a Na^+- and Cl^--dependent transporter and, with respect to its three apparent substrates, both partially random sequential as well as ordered mechanisms have been reported. Here we describe some of the features of DAT, such as the coupling of energy to concentrate dopamine and the properties of slippage and leakage. Further, in considering the regulation of transport velocities by DAT few have considered issues related to substrate regulation of DAT activity. Specifically, what effect do changes in the constants (K) for the participation of Na^+ and Cl^- have on dopamine transport velocity? It is shown that DAT may possess properties of slippage, an argument is made that leakage may be important in neuronal systems containing DAT, and the influence of changing values of *K* for the participation of Na^+ and Cl^- in transport is shown to produce large effects on DAT activity depending on the multisubstrate kinetic mechanism.

Keywords: DAT (Dopamine transporter); Multisubstrate mechanisms; Leakage; Terreactant mechanisms; Na^+-dependent transporter; Cl^--dependent transport; Slippage

1. Introduction

Extracellular water-soluble, polar and/or charged chemical species have virtually no permeability to cell membranes. Thus, cells have evolved specialized molecules within their membranes to catalyze the movement of important ions and compounds across the cell membrane (Amara, 1998; Quick, 2002; Stein, 1986, 1990; Weiss, 1996; Yudilevich et al., 1991). One class of these molecules is known as membrane transporters, which are transmembrane spanning proteins that serve to provide a low resistance path across the cell membrane for external solutes. The transporters can simply provide a diffusion path for a solute to run down its concentration gradient (facilitated diffusion) or the process can be coupled to another energy source (Na^+ gradients and/or hydrolyses of ATP) to concentrate an ion or molecule against a concentration gradient. The treatises cited above can be consulted for the many details of transmembrane transporters in general.

1.1. The neuronal transporter for dopamine

The neuronal dopamine transporter (DAT) is the topic of this presentation. DAT is a Na^+- and Cl^--dependent transporter that mediates the recapturing and concentration of the neurotransmitter, dopamine, into the cell or nearby cells that released it during chemical neurotransmission. Its activity can be regulated by pre-synaptic receptors, protein kinases and membrane trafficking (Batchelor and Schenk, 1998; Chen and Reith, 2000; Meiergerd et al., 1993; Melikian and Buckley, 1999). Pharmacologically, DAT serves as the binding site for the drugs of abuse, cocaine and amphetamine, and the therapeutic agent, Ritalin (methyphenidate). Molecularly the DAT is an 80-kDa protein composed of 12 putative transmembrane spanning regions with the carboxyl and amino termini residing intracellularly. Further, the protein is externally glycosylated, contains consensus sites for phosphorylation, and some membrane spanning regions

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and not others have been found to mediate dopamine binding or co-substrate binding in contradistinction to inhibitor binding (Amara and Sonders, 1998; Amara et al., 1998; Giros and Caron, 1993; Giros et al., 1994).

The nature of the dependence of dopamine transport on Na^+ and Cl^- has been characterized in a number of model systems of the DAT, including synaptosomal preparations of rat striatum (Harris and Baldessarini, 1973; Holz and Coyle, 1974; Kuhar and Zarbin, 1978; McElvain and Schenk, 1992; Wheeler et al., 1993), nucleus accumbens (Povlock and Schenk, 1997) and more recently in cell lines expressing the human dopamine transporter (Chen et al., 1999; Earles and Schenk, 1999). Kinetic mechanisms of DAT have been reviewed recently (Schenk, 2002). The majority of the literature to date suggests that both the rat dopamine transporter (rDAT) and the human dopamine transporter (hDAT) show a first order dependence on both dopamine and Cl^-, and a second order dependence on Na^+. These reaction orders suggest a stoichiometry of 1:2:1, dopamine to Na^+ to Cl^-; however, this is still an object of study (Koshbouei et al., 2003; Schumacher et al., 2000) and is yet to be fully proved by direct chemical measurements. The unbalanced charges suggest that DAT may be electrogenic and this has been shown experimentally in an expression system (Sonders et al., 1997). Differences exist in the proposed kinetic mechanisms (see Fig. 1) of the transport of dopamine between the native rDAT systems (McElvain and Schenk, 1992; Povlock and Schenk, 1997) and the hDAT cell expression system (Chen et al., 1999; Earles and Schenk, 1999). In native rDAT systems (preparations of the striatum and the nucleus accumbens), dopamine uptake follows a partially random sequential binding mechanism, where there is an initial random binding of 1 dopamine molecule and two Na^+ to the transporter then Cl^- binds last

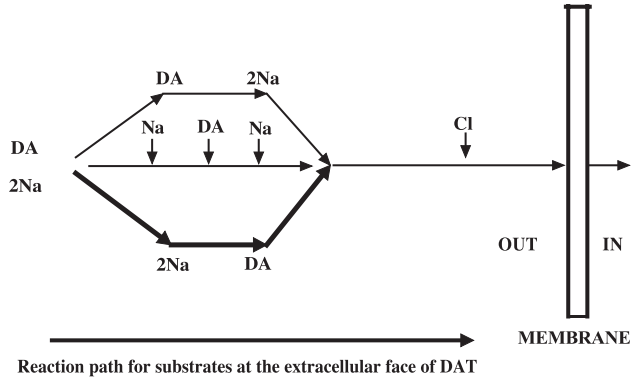

Fig. 1. Multisubstratre mechanisms for rat native DAT and human DAT expressed in human embryonic kidney cells. The reaction path, proceeding from left to right, depicts the binding sequence of the substrates, DA, Na^+ and Cl^- at the extracellular face of DAT. The rat striatum and nucleus accumbens exhibit a partially random sequential mechanism where the two Na^+ and dopamine can bind in any order with Cl^- binding last. The mechanism for dopamine transport at hDAT is ordered and follows the course shown in the lower wings (bolder lines) of the diagram where the two Na^+ bind first before dopamine followed last by Cl^- binding.

and transport occurs (McElvain and Schenk, 1992; Povlock and Schenk, 1997). Conclusions on the transport mechanism for dopamine in preparations of the medial prefrontal cortex have been difficult to make because transport properties in this area differ widely from those in other preparations (Wayment et al., 2001).

For hDAT expressed in a non-neuronal system, transport occurs after the initial ordered binding of two Na^+ and then one dopamine molecule to the transporter followed by Cl^- binding last (Earles and Schenk, 1999). Although hDAT and rDAT are 92% homologous in their amino acid sequence (Giros et al., 1992), it is not known whether the mechanistic differences are due to variations in the transporter protein or a result of the difference between the membrane environment of a neuronal versus a non-neuronal system.

In spite of some questions, it is clear that multisubstrate mechanisms for DAT can be elucidated. So a good question is: How can we use the knowledge of multisubstrate mechanisms to understand the functioning DAT? The goals for this presentation are to (1) examine some of the design properties of DAT in the context of the broader area of transmembrane transporters and (2) review why defining multisubstrate mechanisms is important in the understanding of the function, pharmacology, and regulation of DAT.

2. Comments on the molecular "design" and properties of DAT

The design of a multisubstrate transmembrane transporter should include properties that maximize efficiency and the potential for regulation. Biochemists have introduced a couple of general concepts about the function of transporters that appear to be relevant to DAT. These include maximizing the coupling of co-substrate ion gradients for concentrating substrate (dopamine in the case of DAT) and the properties of *slippage* and *leakage* by which the concentrating property of DAT can be compromised.

DAT activity appears to be able to concentrate dopamine intracellularly by a factor of ca. 10^6 (Earles and Schenk, 1999). The energy required for this feat is thought to be achieved by coupling the out to in movements of dopamine with the Na^+ in to out gradient. The coupling of energy in this manner was postulated in the 1970s (Crane, 1977) and the molecular mechanism by which this occurs is still a topic of current research and discussion (Krupka, 1998, 1999; Stein, 1986).

In neurons the Na^+ gradient, maintained by the Na^+/K^+ ATPase, is about 150-fold, a value three orders of magnitude less than that required for concentrating dopamine. However, DAT functions by exhibiting an apparent 2:1, Na^+ to dopamine ratio, effectively making the energy proportional to the square of the gradient, that is 10^4 to 10^5. If the energy of a ca. -60 mV transmembrane potential and the Cl^- gradient is added the value comes very close to the 10^6 concentrative property of DAT. Thus, an analysis of features

of the multisubstrate apparent stoichiometries and DAT properties can come close to matching that expected by observation of the concentrative properties of DAT. Because clearing extracellular dopamine is essential to terminating dopamine chemical neurotransmission it seems that DAT has "maximized" its use of energy from ion gradients and transmembrane potential to maximize its ability to take up dopamine.

The term *slippage* refers to the translocation of substrate by the transporter that is not coupled to movement of the other co-substrates. For DAT, this would refer to the DAT-mediated movement of dopamine, or Na^+, or Cl^- without the movement of all three. DAT appears to exhibit what might be termed, "dynamic slippage"; that is, under certain conditions, DAT transports dopamine and Na^+ in a stoichiometically coupled manner, whereas under other conditions the relationship is uncoupled and far more Na^+ moves into the cell than at the expected ratio of two Na^+ for each molecule of dopamine. Sonders et al. (1997) showed that DAT can exhibit this property as well and it may play a role in the regulation of DAT activity.

On the other hand, the term "leakage" refers to the movement of a substrate down its concentration gradient without the action of DAT itself. If it is considered that Na^+ is the substrate with the largest out to in concentration gradient then the leakage effect is to short circuit the movement of Na^+ with respect to DAT and reduce DAT activity with regard to transporting dopamine. An analog for this phenomenon with respect to DAT might be that when a neuronal membrane is depolarized Na^+ channels open providing a pathway or pathways for Na^+ inward flux in addition to that of DAT during DAT functioning. The effect would be to reduce DAT activity. However, because DAT is also electrogenic at present it is difficult to discern effects of leakage on DAT-coupled Na^+ gradient from changes in transmembrane potential.

A

$$\frac{v}{V_{max}} = \frac{\frac{[DA][I]^n}{K_m K^n}}{(1+\frac{[I]}{K})^n + \frac{[DA][I]^n}{K_m K^n}}$$

B

$$\frac{v}{V_{max}} = \frac{\frac{[DA][I]^n}{K_m K^n}}{1+\frac{[DA]}{K_m}(1+\frac{[I]}{K})^n}$$

C

$$\frac{v}{V_{max}} = \frac{\frac{[DA][I]^n}{K_m K^n}}{(1+\frac{[DA]}{K_m})(1+\frac{[I]}{K})^n}$$

D

$$\frac{v}{V_{max}} = \frac{\frac{[I]^n}{K'}}{\left(1+\frac{K_m}{[DA]}\right)\left(1+\frac{[I]^n}{K'}\right)}$$

Fig. 2. The mathematical models for various binding sequences. The equations shown are for models of multiple essential activation of DAT as originally described for enzymes by Segel (1993) with the equation numbers from this reference indicated. Key: (A) noncooperative random binding of *n* ions of I before DA binding (Eq. (VII-42)); (B) noncooperative binding of DA first, then *n* ions of I (see Eq. (VII-43)); (C) noncooperative, completely random binding of DA and *n* ions of I (see Eq. (VII-44)); (D) cooperative, random binding of DA and *n* ions of I (see Eq. (VII-47)). In each equation, I = the ion of interest, n = the stoichiometry (or reaction order), DA = dopamine, v = velocity of inward DA transport, V_{max} = the maximal transport velocity of dopamine by DAT, K_M = concentration of DA when the velocity of transport is half of V_{max} and K=[I] when the transport of DA is half maximal.

3. The effects of different multisubstrate mechanisms on dopamine transport

3.1. Rationale and approach to evaluating the effects of different multisubstrate mechanisms

The shape of [DA] versus DAT activity profiles will determine the timing and magnitude of extracellular dopamine concentration changes during chemical neurotransmission. These features define the kinetics and degree of pre- and post-synaptic receptor occupation. A number of binding schemes are possible for dopamine binding to DAT and its other two substrates. The substrates can all bind randomly, some combination of two substrates can bind randomly with the third in some defined relative order, or the three can bind in a defined order. Fig. 2 lists the mathematical expressions for these possibilities for essential catalytic activation of an enzyme or transporter by substrates (Segel, 1993). The models of essential activation require that the substrates considered have to be bound before transport occurs and this is indeed what has been observed experimentally (McElvain and Schenk, 1992; Povlock and Schenk, 1997; Earles and Schenk, 1999). Note that, for completeness, Fig. 2 contains all of the possibilities however only the mechanisms relevant to DAT will be considered in the following discussion.

The challenge is to predict the shapes of the curves of transport velocity of dopamine as a function of extracellular co-substrate concentration and/or its value of K. These shapes cannot be easily seen by inspection because the terms for the concentrations and binding constants appear in both the numerator and the denominator (see Fig. 2). Thus, sample curves were calculated. Profiles of the transport velocity (v) of dopamine versus [DA], $[Cl^-]$, $[Na^+]$, K_{Cl} and/or K_{Na} were calculated using the relevant expressions for the different mechanisms from Fig. 2, a range of K

values from the literature, and the commercially available software package (Prism 2.0, Graphpad Software, San Diego, CA, USA). How the parameters were used is indicated in the legend of each figure for each result.

This exercise has two goals: to show the velocity of dopamine transport is influenced differently between mechanisms and to provide a basis for observing the potential for substrate regulation in one mechanism or another.

3.2. Results of the differing velocity profiles for the multisubstrate mechanism

Cl^- is the substrate that binds last in the kinetic mechanisms under consideration, and Fig. 3 illustrates the effects of Cl^- and K_{Cl} on dopamine transport velocity. The upper panel (A) shows that the Cl^- saturation curve shifts to more positive values with increasing values of K_{Cl}. The lower panel (B) shows that the apparent V_{max} of dopamine transport is changed as a function K_{Cl}; as K_{Cl} increases at a fixed physiological level of Cl^- the apparent V_{max} decreases.

Na^+ has been observed to participate in a random as well as an ordered relationship to the binding of dopamine. Fig. 4 illustrates the differing effects of dopamine transport in the ordered (Panel A) versus random binding (Panel B) models as a function of the degree of DAT saturation (from 10-fold below K_m to 10-fold above K_m) by dopamine at a fixed value of K_{Na}. At physiological levels of Na^+, the ordered binding mechanism exhibits a greater dependency (21-fold versus 12-fold) on Na^+ than the random binding model; however, the random binding model exhibits a steeper change in dopamine transport velocity as a function of $[Na^+]$.

Fig. 5 illustrates the effects of differing values of K_{Na} on the Na^+-dependent saturation curves for dopamine transport by DAT in the ordered (Panel A) versus random binding (Panel B) models. The ordered model exhibits a much more blunted effect (10% reduction versus a factor of 2) due to changes in K_{Na} than the random binding model.

Fig. 6 shows how the velocity of dopamine transport by DAT is affected by the degree of saturation of DAT by

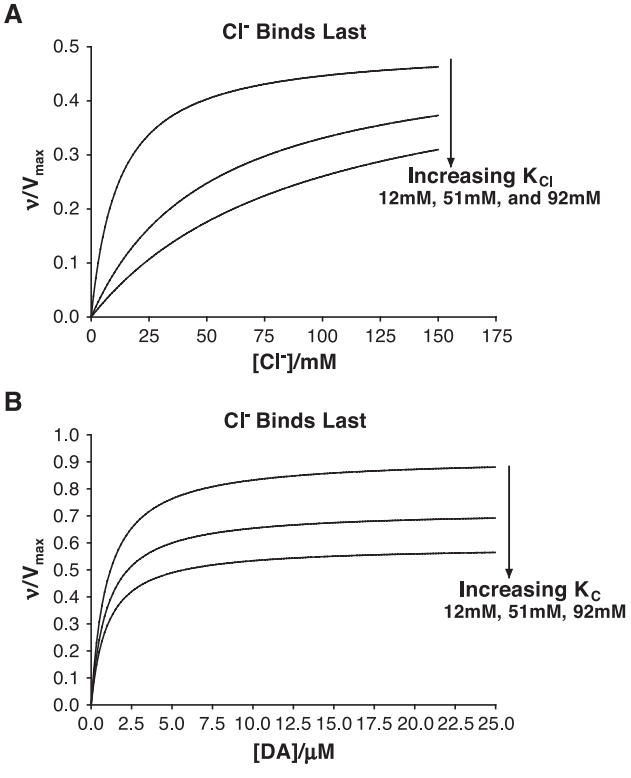

Fig. 3. The effects of the values of K_{Cl} on the [Cl]-dependent and [DA]-dependent transport velocities of DAT using the model of Cl^- binding last, expression B of Fig. 2. In Panel A, each curve was calculated by fixing the K_{Cl} at the indicated value and varying $[Cl^-]$. In Panel B, the $[Cl^-]$ was fixed at the level of physiological buffer and [DA] and K_{Cl} was varied. The K_m for dopamine was fixed at 1.0 μM.

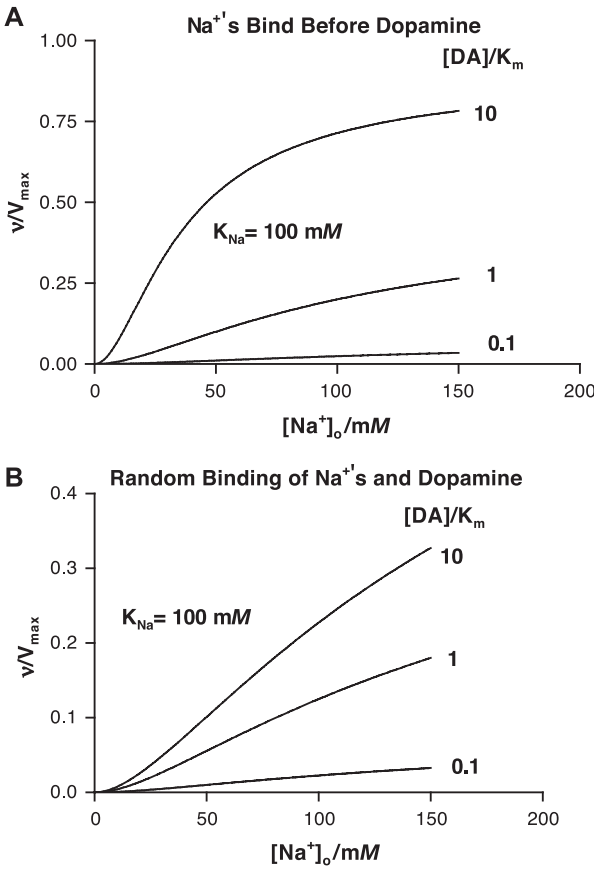

Fig. 4. Influence of varying degrees of saturation of DAT by dopamine for $[Na^+]$-dependent transport of dopamine. Profiles were calculated from models A (ordered) and C (random) from Fig. 2. For the calculations the K_{Na} was held constant at 100 mM, an average value for native DAT. (A) Shows the influence of the ordered binding mechanism on the Na^+ dependence of DA transport when the DA saturation level of the transporter ($[DA]/K_m$) is varied. (B) Shows the influence of the random binding order mechanism on the Na^+ dependence of DA transport when the $[DA]/K_M$ is varied. The Na^+ dependence of dopamine transport velocities are more affected by changing the degree of DAT saturation by dopamine with the ordered binding mechanism than with the random binding order mechanism when the $[DA]_o$ is varied.

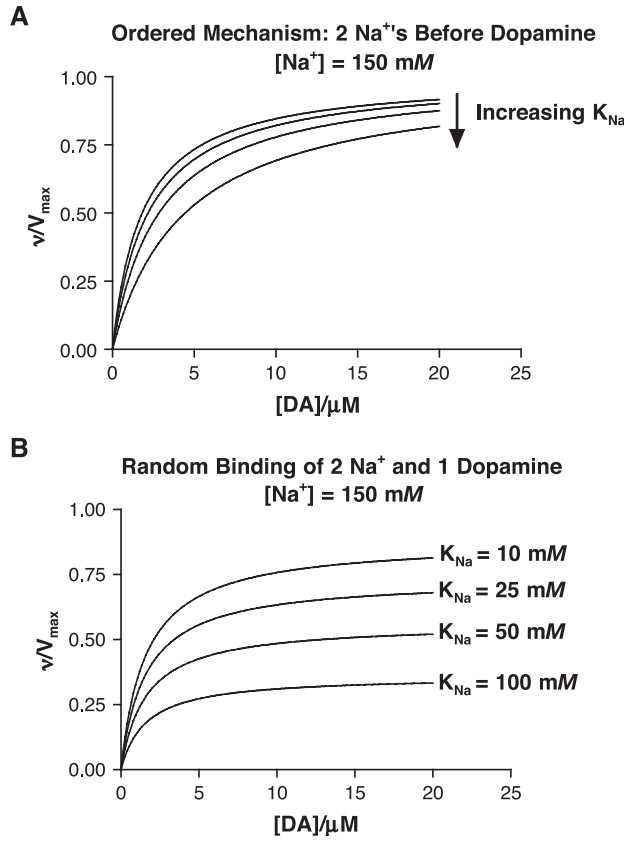

Fig. 5. Influence of K_{Na} on the transport of DA as a function of [DA]. For these calculations, using the same models and in Fig. 4 where the extracellular [Na^+] was held constant at the physiological level of 150 mM, K_m at 1.0 μM and the [DA] was varied. Key: (A) Shows the influence of the ordered binding mechanism on DA transport when the K_{Na} is varied. (B) Shows the influence of the random binding order mechanism on DA transport when the K_{Na} is varied. Dopamine transport velocities are affected more by the random binding order mechanism than the ordered binding mechanism when K_{Na} is varied and the [Na^+] is held at physiological levels.

dopamine and values of K_{Na}. The change in DAT activity as a function K_{Na} is much greater in the random binding model than the ordered binding model.

4. Comments on substrate regulation of DAT activity

It appears from these considerations that a number of different mechanisms could be employed to effect substrate regulation of DAT activity. A regulatory change in the value of K for a given co-substrate could produce a significant change in the activity of DAT. Presumably, this change in K would be the result of a change in phosphorylation or other covalent modification of the DAT protein itself. Na^+ should probably be considered first as the ion whose participation in dopamine transport should be regulated because it is the ion whose gradient provides most of the transport energy.

Stein (1986) in considering how the binding order of substrates influences the efficiency of transport suggests that the ordered mechanism produces the most efficient transport. Our results here showing that the partially random, sequential mechanism exhibits the greatest change with respect to co-substrate values of K may suggest that it is this later mechanism that offers the widest range or greatest number of possibilities for regulation of DAT activity.

An induced change in the multisubstrate mechanism of transport by a change in relative K values may also be a regulatory mechanism employed by transporters. Indeed, examples of this phenomenon are known in enzymology (Segel, 1975) and there is no a priori reason to believe that transporters will not be found to exhibit this property.

In considering DAT pharmacology, the effects of a drug on one co-substrate or another would produce differing

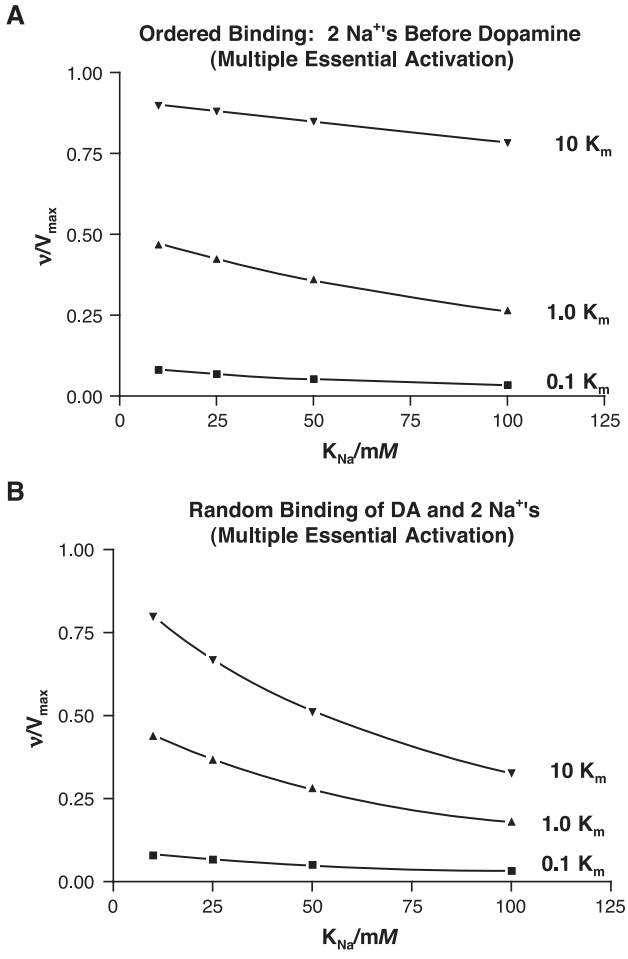

Fig. 6. Influence of K_{Na} on the transport of DA at varying degrees of saturation of DAT by dopamine. Profiles of DA transport velocities (v) normalized for maximal DA transport (V_{max}) versus K_{Na} were calculated as described in the text. For these calculations and profiles, the [Na^+] was held constant at 150 mM. (A) Shows the influence of the ordered binding mechanism on DA transport when the $[DA]_o$ is varied. (B) Shows the influence of the random binding order mechanism on DA transport when the $[DA]_o$ is varied. Dopamine transport velocities are affected more by K_{Na} in the random binding order mechanism than the ordered binding mechanism when the $[DA]_o$ is varied.

results. In order to elucidate these effects, an experimenter would have to conduct multisubstrate analyses. For example, in some studies cocaine has been found to competitively inhibit Na^+ as a co-substrate at DAT (McElvain and Schenk, 1992; Wheeler et al., 1993). Thus, to fully understand drug effects at DAT multisubstrate features of its function have to be taken into consideration.

Thus, examination of multisubstrate mechanisms of DAT activity offers insights into how chemical neurotransmission might be regulated by DAT and serves as a basis for understanding DAT pharmacology.

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