

On reaction dynamics at dopamine synapses

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Abstract

Dopamine neurons play a key role in normal and pathological cognitive processes as well as in the effects of certain drugs of addiction. Models of the synapses of such neurons include transporter mechanisms and reaction dynamics. We focus attention on the fundamental reaction which converts tyrosine to DOPA, which involves a cofactor. The Michaelis-Menten formula for the rate of an enzymatic reaction is modified by the presence of cofactors, which may be either essential or non-essential. In the essential case, the reaction rate is found to depend on the relative magnitudes of the concentrations of the primary enzyme and the cofactor. The case of a non-essential cofactor is more complex and it is shown how this leads to reaction rate formulas which depend explicitly on the concentrations of the enzyme and cofactor. The speed of reaction formulas are applied to the above-mentioned reaction with tyrosine hydroxylase as enzyme and bipterin as cofactor. The results are useful in constructing accurate models of dopamine synapses.

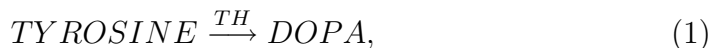
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1 Introduction

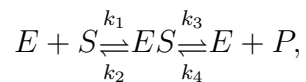
The activities of central dopaminergic neurons have been found to play key roles in both normal [1-4] and pathological [3,5,6] cognitive processes as well as in the effects of several drugs of addiction [1,3,7,8]. Hence there has been a concerted effort to understand through both experimental and theoretical approaches the properties of dopamine neurons and their synapses [9-16]. The theoretical models employed have different emphases, some neglecting most of the neurochemistry [23], some including a including a few of its details [14], whereas others contain a large number of details [15].

In the accurate modeling of dopamine synapses it is important to take into account various chemical reactions including transporter mechanisms for reuptake of dopamine. Fundamental is the production of DOPA (dihydroxyphenylalanine) from tyrosine which arrives in synaptic terminals by axon transport. The basic reaction is



where TH is the enzyme tyrosine hydroxylase. DOPA is then rapidly converted to dopamine by means of the enzyme dopa-decarboxylase. However, according to [17], the activity of TH is relatively feeble and a cofactor, biopterin, (tetrahydrobiopterin, BH-4) is required to make the reaction proceed rapidly enough. There are several other factors which influence the activity of TH [18], including inhibition by free dopamine which competes with biopterin for binding sites on the enzyme. Furthermore, molecular oxygen and iron are required [19,24], but we will only be concerned with the form of the kinetic equations for the core reaction (1) where BH-4 plays a cofactor role.

In the classical scheme, if S is a substrate, E an enzyme and P a reaction product according to



the classical Michaelis-Menten formula [20] for the rate of production, $d[P]/dt$, of the end product is

$$v = \frac{v_{max}}{1 + \frac{K_m}{[S]}}, \quad (2)$$

where $v_{max} = k_3[E]_T$ is the maximum rate, $[E]_T$ is the total (initial) enzyme concentration, and $K_m = \frac{k_2+k_3}{k_1}$ is the Michaelis constant. It has been assumed that the term involving k_4 is negligible, otherwise there are extra terms involving $[P]$ [22]. Time-dependent solutions for the concentrations of all components may be found numerically and it is usually supposed that the enzyme occurs in much lower concentration than the substrate.

Derivation of formula (2), is given in, for example, [21], but there are many reaction schemes where the formula (2) does not apply, such as when there is a cofactor present. In neurochemical applications it is important to study how cofactors affect the basic theory and we will demonstrate how the reaction rates depend on the concentrations of the cofactor and the primary enzyme and also on the reaction schemes underlying the mechanisms of action of the cofactor. We will examine two such reaction schemes and illustrate the usefulness of the results by applying them to the above reaction (1) which is a basic component of several dynamical models of dopaminergic synapses. In a later article we will present a more complex mathematical model, including many types of dopamine receptors.

2 Reaction rates with cofactors

The functioning of many enzymes requires or is accelerated by the presence of small amounts of substances called cofactors. Here we consider a division of cofactors into two types: (a) essential cofactors, where the primary enzyme does not or cannot function without the presence of the cofactor, with which it must first react to form an effective enzyme-cofactor complex; and (b) non-essential cofactors without which a primary enzyme may function but whose functioning is enhanced when binding of a cofactor and primary enzyme occurs to form a complex.

2.1 An essential cofactor

Let K denote the cofactor, E the primary enzyme, S the substrate and P the end product. Then in the case where the cofactor is essential we have the following two reaction schemes,



The cofactor must combine with the primary enzyme in order to produce an effective enzyme complex, KE . The latter then forms an intermediate complex KES which gives rise to the product P .

Now the rate of production of product P is

$$v = d[P]/dt = k_3[KES] \quad (5)$$

as it is assumed that $k_4[P][KE]$ is negligible. Let the total concentrations of enzyme and cofactor be $[E]_T$ and $[K]_T$, respectively. As usual, the maximal value of v occurs when $[KES]$ attains its maximal value, but the value of this maximum depends on the relative magnitudes of $[E]_T$ and $[K]_T$.

By the usual steady state assumption [21] that $d[KES]/dt = 0$ and neglecting the term in k_4 we have

$$[KES] = \frac{[KE][S]}{K_m},$$

where K_m is as before. As it is also assumed that $d[KE]/dt = 0$, we can put

$$[KE] = \frac{[K][E]}{K_K} \quad (6)$$

where we define $K_K = k_{2,K}/k_{1,K}$.

We distinguish two cases. In the first case, (i), the total cofactor concentration is less than or equal to the total primary enzyme concentration; that is $[K]_T \leq [E]_T$; whereas in the second case, (ii), $[K]_T > [E]_T$.

Case (i), $[K]_T \leq [E]_T$. In this case the maximal velocity of the reaction must be proportional to the total concentration of the cofactor K because there may always be some E left over. Thus the maximal value of $[KES]$ is $[K]_T$ so that

$$v_{max} = k_3[K]_T = k_3([K] + [KE] + [KES]).$$

This yields

$$\frac{v_{max}}{v} = \frac{[K]_T}{[KES]} = 1 + \frac{[KE]}{[KES]} + \frac{[K]}{[KES]}. \quad (7)$$

Using the definitions of K_m and K_K we obtain

$$\frac{v_{max}}{v} = 1 + \frac{K_m}{[S]} \left(1 + \frac{K_K}{[E]} \right).$$

The final result for the reaction speed at substrate concentration $[S]$ and enzyme concentration $[E]$ is

$$v = \frac{v_{max}}{1 + \frac{K_m}{[S]} \left(1 + \frac{K_K}{[E]} \right)}. \quad (8)$$

We now consider the second case.

Case (ii), $[K]_T > [E]_T$. Here the maximal reaction rate, given by the maximal value of $k_3[KES]$ must be $k_3[E]_T = k_3([E] + [KE] + [KES])$. Thus

$$\frac{v_{max}}{v} = \frac{[E]_T}{[KES]} = 1 + \frac{[KE]}{[KES]} + \frac{[E]}{[KES]}.$$

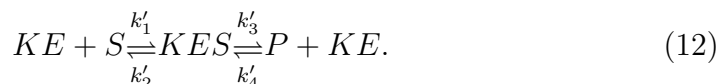
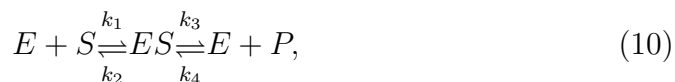
Simplifying further gives, on inversion and rearrangement,

$$v = \frac{v_{max}}{1 + \frac{K_m}{[S]} \left(1 + \frac{K_K}{[K]} \right)}. \quad (9)$$

In either case the expressions have the feature that $\frac{K_m}{[S]}$ in the original Michaelis-Menten expression is multiplied by a factor of the form $1 + X$. For the case of an essential cofactor, case (i), with $[K]_T \leq [E]_T$ we see from (8), $X = \frac{K_K}{[E]}$ so that as $[E] \rightarrow \infty$ we have $X \rightarrow 0$ and v increases to eventually attain the usual Michaelis-Menten form. Similarly, when the cofactor is essential (case (ii) and $[K]_T \geq [E]_T$) we see from (9) that $X = \frac{K_K}{[K]}$ so $X \rightarrow 0$ as $[K] \rightarrow \infty$ and again in the limit the Michaelis-Menten form is attained. The formula for case (ii) has been previously employed at dopamine synapses in [14]. We now turn to the case in which the reaction proceeds with or without a cofactor.

2.2 The cofactor is non-essential

Suppose that E and EK both function enzymatically but with different efficacies, that of EK being expected to be greater. Thus we have the three reactions



Consideration of the steady states gives, ignoring contributions from k_4 and k'_4 ,

$$\frac{[E]}{[ES]} = \frac{K_m}{[S]}, \quad \frac{[KE]}{[KES]} = \frac{K'_m}{[S]}, \quad \frac{[K][E]}{[KE]} = K_K, \quad (13)$$

where

$$K'_m = \frac{k'_2 + k'_3}{k'_1}, \quad K_K = \frac{k_{2,K}}{k_{1,K}}. \quad (14)$$

By the standard arguments we find that the reaction speed is given by the following formulas.

Case (i), $[K]_T \leq [E]_T$. In the case where the cofactor concentration is less than the enzyme concentration, there can be, at maximal reaction rate, left over E to produce P without any K . We introduce the parameter $\alpha = k'_3/k_3$,

which describes the relative efficacies of KES and ES in producing the product P , and assume $\alpha \gg 1$. It can then be shown that the reaction speed is approximately

$$v \approx \frac{v_{max}}{1 + \frac{K_m}{[S]} \left(1 + \frac{K_K}{[E]}\right) + \frac{1}{\alpha} \left(1 + \frac{K'_m}{[S]} + \frac{K_K K'_m}{[K] K_m}\right)}. \quad (15)$$

In the event that the second term in the denominator is also negligible compared to the first, then (15) reduces to

$$v \approx \frac{v_{max}}{1 + \frac{K_m}{[S]} \left(1 + \frac{K_K}{[E]}\right)}$$

which is in fact (8), corresponding to the case in which the cofactor is essential. This is a useful consistency check because $\alpha \gg 1$ implies that the enzyme acting by itself without the cofactor is very feeble compared to its acting with the cofactor.

Case (ii), $[K]_T > [E]_T$. In this case, after some substitutions and simplifications, the reaction speed is found to be

$$\frac{v}{v_{max}} = \frac{1}{\left(1 + \frac{K'_m}{[S]} \left(1 + \frac{K_K}{[E]}\right)\right)} + \frac{1}{\alpha \left(\frac{[K]}{K_K} \left(1 + \frac{K'_m}{[S]}\right) + \frac{[K] K'_m}{[E] [S]}\right)}. \quad (16)$$

3 Application at dopamine synapses

We now turn our attention to reactions occurring at dopamine synapses. Mathematical models of such synapses have included the chemical kinetics of various reactions and transport processes [14,15]. In the synaptic terminals tyrosine is the substrate (S), the enzyme (E) being tyrosine hydroxylase, denoted by TH , and the end product is dihydroxyphenylalanine (DOPA). The cofactor, biopterin, is required to make the reaction proceed rapidly enough. Let $[K]$ be the concentration of the cofactor biopterin which, as in [14,15], we assume is an invariant. Let $[TYR]$ be the concentration of tyrosine which is also assumed constant in the synaptic terminal due to replenishment by axonal flow, and let $[TH]$ be the concentration of tyrosine hydroxylase. If the cofactor is essential then the rate of production of DOPA for the case in

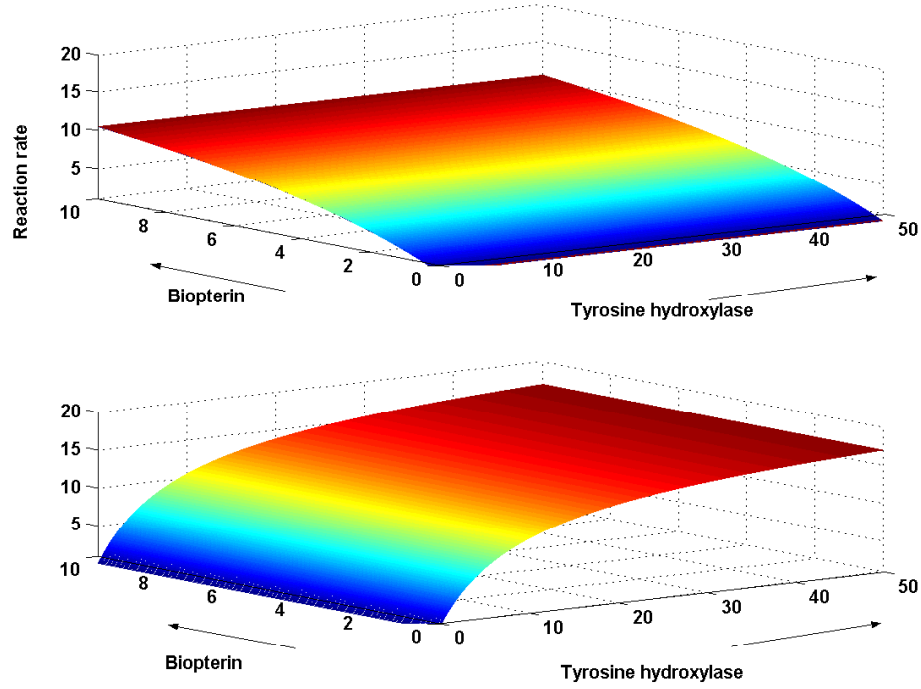


Figure 1: The reaction rate for conversion of tyrosine to DOPA using the individual formulas (17) (bottom drawing) and (18) (top).

which the enzyme concentration is greater than that of the cofactor is given by

$$\frac{d[DOPA]}{dt} = \frac{v_{max}}{1 + \frac{K_m}{[TYR]} \left(1 + \frac{K_K}{[TH]}\right)}. \quad (17)$$

In the case that the bioperin has a greater concentration than tyrosine hydroxylase, the reaction rate is

$$\frac{d[DOPA]}{dt} = \frac{v_{max}}{1 + \frac{K_m}{[TYR]} \left(1 + \frac{K_K}{[K]}\right)}. \quad (18)$$

The latter is the basis of previous models, but a different result would be obtained if (17) is employed. To illustrate we have calculated reaction rates

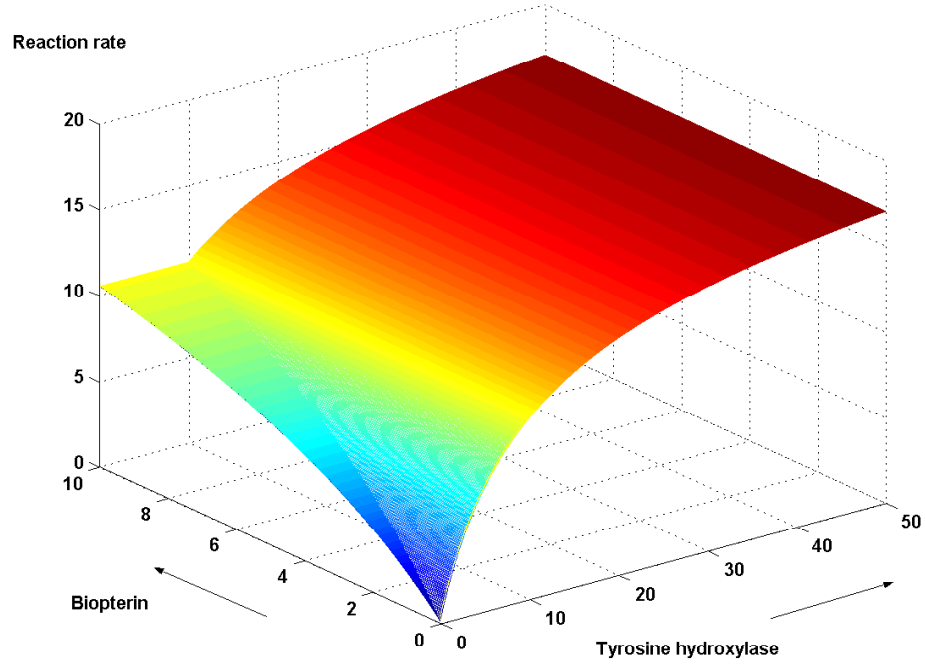


Figure 2: Reaction rate for the conversion of tyrosine to DOPA using appropriate formulas in the appropriate ranges of concentrations.

over ranges of concentrations using some known data on this reaction [14,15]: $v_{max} = 20$ nmol/g/min; $K_m = 0.04$ nmol/g; $[TYR] = 444$ nmol/g; $K_K = 10^5$ nmol/g. The value of $[K]$ was given as 1 nmol/g and this is included in the range of values for which v was calculated: $K \in [1, 10]$ and $TH \in [1, 20]$. The results for the different formulas (17) and (18) are given in Figure 1 and the (correct) combination of formulas is shown in Figure 2. However, according to [17], the enzyme is effective by itself, albeit less strongly. This suggests that biopterin can be classified as a non-essential cofactor. Then if the biopterin concentration is less than that of tyrosine hydroxylase, the rate is approximately

$$\frac{d[DOPA]}{dt} \approx \frac{v_{max}}{1 + \frac{K_m}{[TYR]} \left(1 + \frac{K_K}{[TH]}\right) + \frac{1}{\alpha} \left(1 + \frac{K'_m}{[TYR]} + \frac{K_K K'_m}{[K] K_m}\right)}. \quad (19)$$

On the other hand, if the biopterin has a greater concentration than that of tyrosine hydroxylase we have

$$\frac{v}{v_{max}} = \frac{1}{\left(1 + \frac{K'_m}{[TYR]} \left(1 + \frac{K_K}{[TH]}\right)\right)} + \frac{1}{\alpha \left(\frac{[K]}{K_K} \left(1 + \frac{K'_m}{[TYR]}\right) + \frac{[K]K'_m}{[TH][TYR]}\right)}. \quad (20)$$

In [14] the effects of two competitive inhibitors of tyrosine hydroxylase were included, but see also [15] where the treatment was different. Including the inhibitors makes the expressions for the rate of production of DOPA more complicated than the ones we have described above for the core reaction. Since quantities of interest include the equilibrium points for the system of differential equations modeling the dynamics of dopamine synapses, the solutions obtained can be substantially different if the system is based on (17) (or (19)) instead of (18) (or (20)). For example, $1 + \frac{K_K}{[K]}$ is expected to be larger than $1 + \frac{K_K}{[TH]}$. A detailed quantitative analysis will be reported in a forthcoming article.

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