

Dynamical Models of Central Nervous System Synapses : The Role of Chemical Kinetic Theory.

Henry C. Tuckwell

Institute for Advanced Studies
Australian National University
Canberra ACT 0200 Australia

In order to construct models for the dynamical operation of central nervous system synapses, accurate chemical kinetic theory is required for enzymatic reactions in order to find equilibrium points when neurochemistry and neurotransport processes are included. Such modelling in conjunction with receptor dynamics is important for analyzing various behavioural states, such as depression and schizophrenia, of interest in psychiatry^{1,2,3} and the effects of drugs on these equilibrium points⁴. Of central importance are reactions involving, for example, neurotransmitters and their precursors, which are mediated by enzymes and cofactors. We have developed kinetic equations for such reactions and applied them to give a new formalism for quantitative analysis illustrated by the conversion of tyrosine to DOPA.

Let S be a substrate, E an enzyme and P be reaction product in the classical scheme



Then the Michaelis-Menten formula for the rate of reaction is

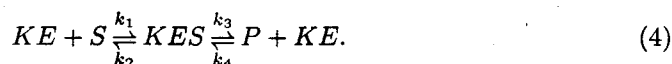
$$v = \frac{v_{max}}{1 + \frac{K_m}{(S)}}, \quad (2)$$

where v_{max} is the maximum possible rate, $K_m = \frac{k_2 + k_3}{k_1}$, and (S) denotes the concentration of S . Derivation of formula (2) can be found, for example, in reference 5. When the simple scheme (1) does not apply, formula (2) must be appropriately modified.

Complex models of dopaminergic synapses have been proposed^{6,7,8} consisting of systems of differential equations and incorporating modified Michaelis-Menten formulas due to competitive inhibitors and cofactors as well as various transport processes. However, there is a need to reconsider how cofactors alter the basic Michaelis-Menten theory.

It is well known⁹ that the proper functioning of many enzymes requires the presence of cofactors. These may be either (a) essential, in which case the primary enzyme does not function without the presence of the cofactor, with which it must first react to form an effective enzyme-cofactor complex; or (b), non-essential, where the enzyme may function alone but functioning is enhanced when binding of cofactor and primary enzyme occurs.

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,



We follow the usual approach via steady states and have^{5,9} $\frac{(K)(E)}{(KE)} = K_K$, where $K_K = \frac{k_{2,K}}{k_{1,K}}$, and $\frac{(KE)(S)}{(KES)} = K_m$, where K_m is as before.

Suppose as expected the cofactor concentration is less than that of the primary enzyme. The maximal velocity of the reaction is proportional to the total concentration of K because there may always be some E left over. Now, the total concentration of K is given by $(K_{tot}) = (K) + (KE) + (KES)$. The maximal velocity must be proportional to (K_{tot}) and the speed at less than maximal values must be proportional to the concentration of the intermediate complex KES . Denoting the speed of reaction by v and the maximal speed by v_{max} , we find

$$v = \frac{v_{max}}{1 + \frac{K_m}{(S)} \left(1 + \frac{K_K}{(E)}\right)} \quad (5)$$

This can be compared with the Michaelis-Menten formula (2) which it approaches as $(E) \rightarrow \infty$ for fixed (S) . In the event that $(K) \geq (E)$, the maximal reaction rate must be determined by (E_{tot}) and we have

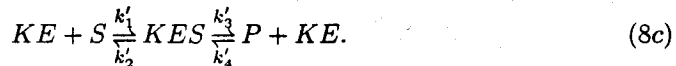
$$\frac{v_{max}}{v} = \frac{(E_{tot})}{(KES)} \quad (6)$$

which leads to

$$v = \frac{v_{max}}{1 + \frac{K_m}{(S)} \left(1 + \frac{K_K}{(K)}\right)} \quad (7)$$

Equation (7) is the basis of the models previously employed for dopaminergic synapses^{6,7}.

If we now let both E and EK be effective in the enzymatic process but with different efficacies, that of EK being expected to be greater, we must consider the trio,



In the case where (K) is less than (E) we find, since

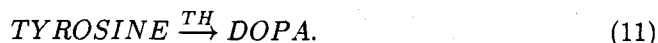
$$v_{max} = k'_3(K_{tot}) + k_3((E_{tot}) - (K_{tot})), \quad (9)$$

that

$$v = \frac{v_{max}}{\frac{(k'_3 - k_3) \left[1 + \frac{(E)}{K_K} \left(1 + \frac{(S)}{K_m} \right) \right]}{\frac{(E)}{K_K} \left(k_3 + k'_3 \frac{(S)}{K_m} \right)} + \frac{k_3 \left[1 + \frac{(S)}{K_m} + \frac{(K)}{K_K} \left(1 + \frac{(S)}{K'_m} \right) \right]}{\left(k'_3 \frac{(K)(S)}{K_K K'_m} + k_3 \frac{(S)}{K_m} \right)}} \quad (10)$$

where $K'_m = \frac{k'_2 + k'_3}{k'_1}$. In cases where the enzyme acting by itself is extremely feeble, so that $k'_3 \gg k_3$, this formula reduces to (7). In the case $(K) \geq (E)$ for a non-essential cofactor again a modified formula is obtained for v .

Models of dopaminergic synapses have included the chemical kinetics of various reactions in the sequence of chemical and transport processes which occur at such synapses. In the synaptic terminal, tyrosine, S, is the substrate for the enzyme tyrosine hydroxylase, TH, in the production of dihydroxyphenylalanine, DOPA:-



However the activity of TH is relatively feeble and a *biopterin* cofactor is required to make the reaction proceed rapidly enough¹⁰. This reaction forms one of the components of the models of dopaminergic synapses^{6,7,8}. Molecular oxygen is implicated in this reaction also¹¹. Subsequent to (11) in the functional neurochemistry of the dopamine synapse is the conversion of $DOPA$ to *dopamine* by means of the enzyme *dopa-decarboxylase*.

In the approaches adopted so far^{6,7,8} the rate of production of $DOPA$ in the core reaction has been of the form of (7)-

$$\frac{d(DOPA)}{dt} = \frac{v_{max}}{1 + \frac{K_m}{(TYR)} \left(1 + \frac{K_K}{(K)} \right)}, \quad (12)$$

where (K) is the concentration of the cofactor, *biopterin*. The concentration of cofactor was assumed to be an invariant.

If the cofactor is assumed to be essential, and since $(K) < (TH)$ should apply, then, instead of (12) we should, according to the above results employ the formula

$$\frac{d(DOPA)}{dt} = \frac{v_{max}}{1 + \frac{K_m}{(TYR)} \left(1 + \frac{K_K}{(TH)} \right)}. \quad (13)$$

However, although TH is effective by itself, it is not so effective as with the cofactor. Thus we should employ the results for a nonessential cofactor. The rate of change of the $DOPA$ concentration should then be given by the complex expression (10) with $E = TH, S = TYR$ and K as the *biopterin* cofactor.

It is clear that if the equilibrium points of the system of equations used to model a dopaminergic synapse are sought, then the solutions obtained will be substantially different if the system is based on the assumption that (13) rather than (12) is appropriate for the core reaction. Similarly, if one employs the more complex expression (10), possibly modified by the existence of competitive inhibitors⁶ and other important components of a dynamical model of a synapse such as pumps, then one will obtain a quite different set of solutions for the equilibrium points.

Despite the fact that the cofactor concentration is usually less than that of the enzyme, formula (12) for the opposing case has formed the basis of models designed to quantitatively study the dynamics of dopaminergic synapses. However, it is essential to have accurate kinetic theory for the sequences of reactions occurring at central nervous system synapses in order to obtain the correct equilibrium points for the corresponding dynamical models.

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