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# Presynaptic control of efficacy of GABAergic synapses in the hippocampus

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**Abstract**

First we found that applying substances that change intracellular presynaptic GABA concentration alter the synaptic efficacy of hippocampal GABAergic neurons. The amplitude as well as the frequency of occurrence of spontaneous postsynaptic currents (mIPSCs) are affected. Then, we developed a model of presynaptic vesicle dynamics to better understand the causal relationship between cytosolic GABA concentration and mIPSC amplitude and frequency. One way to explain our experimental findings is to postulate that the filling of vesicles as well as their transition into the readily releasable pool depends on vesicular GABA content. 

*Keywords:* Synaptic plasticity; Metabolism; Vesicle cycle; Readily releasable pool

## 1. Biological basis

Inhibitory synaptic interaction in the mammalian brain requires the release of $\gamma$–amino butyric acid (GABA) from presynaptic vesicles of specialized neurons where the transmitter is stored at high concentrations. It has been proposed that a reduction of available GABA can contribute to decreased efficacy of inhibitory transmission during prolonged states of epileptic activity. This is the basis for the anticonvulsant effect of the GABA–transaminase inhibitor vigabatrin ($\gamma$–vinyl GABA) which blocks

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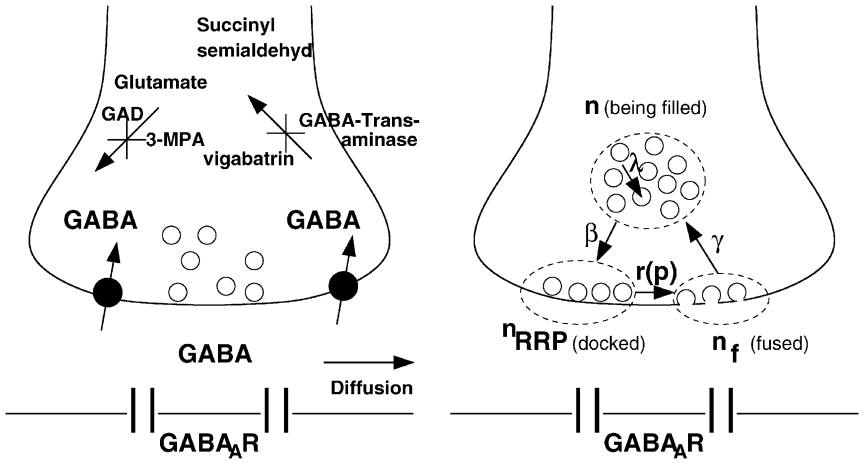


Fig. 1. Left: Overview of presynaptic GABA metabolism: GABA is synthesized by the enzyme glutamic acid decarboxylase (GAD) which can be blocked by 3–mercaptoproprionic acid (3-MPA) and catabolized by GABA–transaminase which in turn can be blocked by vigabatrin. Right: Presynaptic vesicles are modeled in three different compartments linked by the transition rates $\beta$, $r(p)$, and $\gamma$. Vesicles that are neither docked nor fused are filled with a rate $\lambda$.

the catabolic pathway for GABA and thereby enhances the amount of synaptically available GABA. Inversely, GABA concentration can be reduced by the inhibition of the enzyme glutamic acid decarboxylase (GAD) using the proconvulsant substance 3–mercaptoproprionic acid (3-MPA) (Fig. 1).

The cellular mechanisms linking GABA–metabolism and inhibitory efficacy have been explored with patch–clamp recordings of mIPSCs (miniature inhibitory postsynaptic currents) in CA3 pyramidal cells of cultured hippocampal slices. The slices were treated with low concentrations of vigabatrin over 4–5 days or with low concentrations of 3–MPA for 12 h. Amplitude and frequency distributions of spontaneous mIPSCs were analyzed.

The effect of the metabolically altered presynaptic concentration of GABA on the spontaneously occurring mIPSCs is twofold: elevation of presynaptic GABA concentration by vigabatrin causes an increase in the mean amplitude as well as in the mean frequency of occurrence; decrease of presynaptic GABA concentration by 3–MPA has the opposite effect. The change in amplitude can intuitively be explained by an increased level of GABA transport into the vesicles but the enhanced frequency of spontaneous release has been unexpected.

## 2. Mathematical model

For a better understanding of the effects of changes in the presynaptic GABA metabolism, we developed a model of the presynaptic vesicle cycle to relate changes in

amplitude and frequency distributions of mIPSCs to changes in presynaptic GABA concentrations.

The presynaptic model is simplified from the picture developed in [5] and consists of three compartments in which changes due to an elevated or decreased GABA concentration may occur. We model the time course of vesicle distributions $n(v, t)$ with different GABA content $v$ that are being filled (a), released (b), and recycled (c).

(a) Vesicles are filled by the vesicular GABA transporter (VGAT) with a rate $\lambda$ and pass over to the readily releasable pool (RRP) with a rate $\beta$. In the following, we will consider different dependencies on GABA for both $\lambda$ and $\beta$.

(b) Vesicles in the RRP are not being filled further but can be released either spontaneously or following an action potential with different probabilities of release. Both rates follow a Poisson process and depend in a non-linear way on the number of vesicles in the RRP. The probability of release $p$ in case of an action potential arriving at the presynaptic bouton has been described in [1,3] as $p = 1 - \exp(-k\hat{n}_{\mathrm{RRP}}^{1.5})$ where $\hat{n}_{\mathrm{RRP}}$ denotes the number of vesicles in the RRP and $k = 0.06$. Typical values for $\hat{n}_{\mathrm{RRP}}$ are $5 \pm 3$ vesicles [5], so the probability for evoked release is about 0.36.

(c) Re-uptake of vesicles is also modeled as a Poisson process with effective rate $\gamma$. The number of recycled empty vesicles contributes to the initial condition $n(0, t)$ for the vesicular filling process $n(v, t)$.

This leads to the following set of partial differential equations describing the presynaptic vesicle cycle

$$\frac{\partial n(v,t)}{\partial t} = -\frac{\partial}{\partial v}[\lambda(v)n(v,t)] - \beta(v)n(v,t), \tag{1}$$

$$\frac{\partial n_{\mathrm{RRP}}(v,t)}{\partial t} = \beta(v)n(v,t) - r(\hat{n}_{\mathrm{RRP}})n_{\mathrm{RRP}}(v,t), \tag{2}$$

$$\frac{\partial n_{\mathrm{f}}(t)}{\partial t} = r(\hat{n}_{\mathrm{RRP}})n_{\mathrm{RRP}}(v,t) - \gamma n_{\mathrm{f}}(t) \tag{3}$$

with the boundary condition $n(0, t) = (\gamma/\lambda)n_{\mathrm{f}}(t)$ and $\hat{n}_{\mathrm{RRP}}(t) = \int_0^\infty n_{\mathrm{RRP}}(v, t)\,\mathrm{d}v$.

## 3. Five scenarios

### 3.1. Only full vesicles dock and $\lambda$ is constant

First, we consider the case where $\lambda$ is constant, i.e. every vesicle is filled with a constant rate $\lambda$ independent of GABA content. In addition, we assume that only vesicles with a defined GABA content $v_{\max}$ can pass over to the RRP. This is not consistent with experimental data.

### 3.2. Both rates $\lambda$ and $\beta$ are constant

Now vesicles with different GABA content cannot only be filled further but also pass over into the RRP (with rate $\beta$ equal for all vesicles). This has the steady-state solution

$$n_{\mathrm{RRP}}(v) = \frac{\beta}{r(\hat{n}_{\mathrm{RRP}})} n(0) \exp\left( -\frac{\beta v}{\lambda} \right). \tag{4}$$

This exponentially decreasing distribution is also inconsistent with experimental data.

### 3.3. All vesicles dock with the same rate and $\lambda = \lambda(v)$

Next, we consider the case where the filling rate $\lambda$ varies with the vesicular GABA content, i.e. $\lambda = \lambda(v)$. This has the steady-state solution

$$n_{\mathrm{RRP}}(v) = \frac{\beta}{r(\hat{n}_{\mathrm{RRP}})} n(0) \frac{\lambda(0)}{\lambda(v)} \exp\left( -\beta \int_0^v \frac{\mathrm{d}v}{\lambda(v)} \right). \tag{5}$$

For reasonable choices of $\lambda(v)$ this can reproduce the amplitude but not the frequency effect.

### 3.4. The docking rate $\beta$ depends on $v$

If we assume a constant filling rate $\lambda$ but allow for a vesicular GABA dependence of the docking rate $\beta$ we obtain for the steady-state distribution of vesicles in the RRP

$$n_{\mathrm{RRP}}(v) = \frac{\beta(v)}{r(\hat{n}_{\mathrm{RRP}})} n(0) \exp\left( -\frac{1}{\lambda} \int_0^v \beta(v)\, \mathrm{d}v \right). \tag{6}$$

For further illustration we choose $\beta(v) = 1 - \exp(-v)$ leading to

$$n_{\mathrm{RRP}}(v) = \frac{n(0)}{r(\hat{n}_{\mathrm{RRP}})} (1 - \mathrm{e}^{-v}) \exp\left[ -\frac{1}{\lambda} (\mathrm{e}^{-v} + v - 1) \right]. \tag{7}$$

This function peaks at $v_{\max} = \ln(2 + \lambda + \sqrt{4\lambda + \lambda^2}) - \ln 2$. So the location of the peak increases with $\lambda$ that way reproducing the amplitude effect. But now the number of vesicles in the RRP $\hat{n}_{\mathrm{RRP}}$ also increases with $\lambda$ resulting in a frequency effect as well.

### 3.5. Both rates depend on $v$

If we now assume both rates $\lambda$ and $\beta$ to be dependent on $v$ we get

$$n_{\mathrm{RRP}}(v) = \frac{\beta(v)}{r(\hat{n}_{\mathrm{RRP}})} n(0) \frac{\lambda(0)}{\lambda(v)} \exp\left( -\int_0^v \frac{\beta(v)}{\lambda(v)}\, \mathrm{d}v \right). \tag{8}$$

To further illustrate this case we choose $\beta(v)$ as above and $\lambda(v) = \lambda_0 \exp(-v)$. This gives

$$n_{\mathrm{RRP}}(v) = \frac{n(0)}{r(\hat{n}_{\mathrm{RRP}})}(1 - \mathrm{e}^{-v}) \exp\left[ v + \frac{1}{\lambda_0}(v + 1 - \mathrm{e}^{v}) \right]. \tag{9}$$

As before, this function peaks at $v_{\max} = \ln(2 + \lambda_0 + \sqrt{4\lambda_0 + \lambda_0^2}) - \ln 2$ showing an amplitude effect but this time the frequency effect is more pronounced (in accordance with our preliminary experimental data).

## 4. Interpretation of $\beta = \beta(v)$

To explain the dependence of the transition rate on vesicular GABA content we propose two alternative hypotheses:

First, one can assume some kind of threshold detection within the docking mechanism: the function of some (unknown) molecule in the vesicular membrane that is necessary for the docking of vesicles could depend on vesicular GABA content. Alternatively, it could instead depend on the pH or proton gradient of the vesicular membrane, assuming this gradient to change during the filling of vesicles with GABA. As of today, there are no biochemical data available to support or reject this hypothesis.

Second, one can assume that the presynaptic membrane contains $\mathrm{GABA_A}$ receptors, which may have a depolarizing effect on the presynaptic membrane potential [4]. It is also known that depolarization-induced increase in presynaptic calcium concentration triggers transition to the RRP [2] and thus leads to an increased number of vesicles in the RRP.

## 5. Summary

*Experimental result*: Amplitude and frequency distributions of spontaneous inhibitory postsynaptic currents (mIPSC) can be shifted experimentally by varying the presynaptic cytosolic GABA concentration.

*Modeling result*: This can be explained by postulating that the transition rate of vesicles into the readily releasable pool depends upon their GABA content. This dependence can be interpreted in at least two different ways.

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