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Synaptic glutamate spillover increases NMDA receptor reliability at the cerebellar glomerulus

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ABSTRACT

Glutamate spillover in the mossy fiber to granule cell cerebellar glomeruli has been hypothesized to increase neurotransmission reliability. In this study, we evaluate this hypothesis using an experimentally based quantitative model of glutamate spillover on the N-methyl-D-aspartate receptors (NMDA-Rs) at the cerebellar glomerulus. The transient and steady-state responses of NMDA-Rs were examined over a physiological range of firing rates. Examined cases included direct glutamate release activation, glutamate spillover activation, and a combination of direct and spillover activation. Our results illustrate that the effects of spillover alone are equivalent to direct release and, notably, combined spillover and direct release effects on NMDA-Rs are not additive. Our results show that spillover does in fact provide a high degree of reliability given that the synaptic vesicle release rate must fall to approximately 15–25% of what is considered the normal baseline level in order to substantially alter neurotransmission across the examined range of frequencies. We suggest that the high reliability provided by activation due to glutamate spillover could be used to conserve energy by reducing the required overall glutamate load at higher frequencies.

1. Introduction

Neurotransmitter spillover has been a topic of special interest over the last decade, with several theoretical and experimental papers identifying its presence at multiple synapse types, including stellate cells (Carter and Regehr, 2000), climbing fibers (Szapiro and Barbour, 2007), purkinje (Huang and Bordey, 2004), and granule cells (Rossi et al., 2002; Cathala et al., 2003; Xu-Friedman and Regehr, 2003; Sargent et al., 2005; Mitchell et al., 2007). In particular, the role of glutamate spillover on the activation of N-methyl-D-aspartate receptors (NMDA-Rs) has been debated. In some cases, spillover activation is thought to be pathological, such as the spillover activation of NMDA-Rs in the spinal dorsal horn, which is associated with neuropathic pain (Nie and Weng, 2010) and especially in the case of excitotoxicity due to neural injury (Mitchell and Lee, 2008). However, in most cases, spillover is thought to be a physiological phenomenon, including the activation of extrasynaptic NMDA-Rs (Asztely et al., 1997; Kullmann and Asztely, 1998; Harney et al., 2008), the activation of climbing fiber interneurons, where spillover is thought to be the sole means of synaptic communication (Szapiro and Barbour, 2007) and especially activation of NMDA and AMPA receptors at the cerebellar glomeruli (D'Angelo et al., 1995; DiGregorio et al., 2002; Cathala et al., 2003; Sargent et al., 2005).

Each cerebellar glomerulus contains a single mossy fiber rosette at its center with up to twenty granule cell dendritic claw contacts followed by a sheath of glial cells surrounding the entire assemblage (Llinas et al., 2004). Given that spillover at the glomeruli has been identified in multiple theoretical (Saftenku, 2005; Mitchell et al., 2007) and experimental studies (D'Angelo et al., 1995; DiGregorio et al., 2002; Cathala et al., 2003; Sargent et al., 2005), the question has moved from "Does spillover physiologically occur?" to "How does spillover impact synaptic transmission?" Based on experimental and theoretical evidence, glutamate spillover at mossy fiber to granule cell synapse has been hypothesized to increase transmission reliability (Otis, 2002; Saftenku, 2005; Sargent et al., 2005), reduce variability (Otis, 2002), synchronize granule cell firing (DiGregorio et al., 2002), and assist in long term potentiation and depression (Nieus et al., 2006), to name just a few possibilities.

The role of NMDAR-s at the glomerulus has been a particular topic of recent interest (Mapelli et al., 2010; Solinas et al., 2010). The role of the NMDA-R at the glomerulus has been difficult to elucidate with different experimental studies showing differing locations of NMDA-Rs (i.e. synaptic versus extrasynaptic) (Yamada, 2001; Petralia et al., 2002; Xu-Friedman and Regehr, 2003), as well as different properties of the glomerulus at different cell ages (D'Angelo et al., 1994; Brickley et al., 1996;

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Cathala et al., 2003). The goal of the current theoretical study was to examine the potential role of synaptic NMDA-Rs at the cerebellar glomerulus in both direct and spillover transmission. We examine the impact of glutamate spillover on NMDA activation at a variety of physiological firing rates over a time course of 10 s using an experimentally based quantitative model (Mitchell et al., 2007; Mitchell and Lee, 2007). Our results indicate that spillover activation alone can be nearly equivalent to direct activation at most frequencies, lending credence to the increased reliability hypothesis. However, our results may suggest that spillover could also be used as a means to conserve energy by reducing the overall glutamate load without sacrificing overall synaptic efficacy.

2. Methods

We utilize our previously published quantitative model of glutamate spillover (Mitchell et al., 2007; Mitchell and Lee, 2007) to determine the temporal glutamate concentration and NMDA-R open probability profiles at a neighbor synapse in the glomerulus. Glutamate diffusion and uptake in the glomerulus is simulated using the Saftenku diffusion model (Saftenku, 2005), and NMDA-R open probabilities are simulated using the Banke and Traynelis NMDA-R model. The methods that are most pertinent to the current study are described below. For additional information on model detail, namely model equations and experimental validation, we refer the reader to Saftenku (2005) and Banke and Traynelis (2003) as well as our previous studies where sensitivity analyses and derivation of parameters, model application, comparison, and limitations have been exhaustively covered (Mitchell et al., 2007; Mitchell and Lee, 2007). To briefly summarize, the spillover model closely matches experimental data examining the EPSC at the glomerulus, and varying parameters within their experimentally determined range, as shown in Table 1, does not substantially alter the model results.

2.1. Diffusion model

The Saftenku cerebellar glomerulus diffusion model (Saftenku, 2005) utilizes a cylindrical geometry to represent glutamate diffusion from a point source that includes neighbor synapse contributions and a simple residence time based method for glutamate uptake to represent the transient glutamate concentration at a neighbor synapse. This model utilizes parameters that have been experimentally determined. Table 1 lists the diffusion model parameter base values, physiological ranges, and references. The most pertinent parameters, which are specific to the cerebellar glomerulus, were determined using experimental electromicrographs from Xu-Friedman and Regehr (2003) taken from rats age 17–21 days.

The geometry of the glomerulus used by the diffusion model is as follows: the glomerulus contains a mossy fiber at its center that is 3–4 μm in diameter (R_{MF}) and 6.5–10 μm in length. The mossy fiber is encapsulated in a glial sheath located approximately 1–1.5 μm from the mossy fiber terminal (Hamori et al., 1997; Xu-Friedman and Regehr, 2003). Assuming that the release sites form a uniform pattern in the circle, r_{MD} is the radius of a circle, which on average contains one release site. This radius is equal to $1/\sqrt{\nu_s\,\Pi}$, where ν_s is the release site density, 1.5–2.3 μm^2 as determined by electromicrographs from Xu-Friedman and Regehr (2003) and others (Sorra and Harris, 1998; Rusakov et al., 1999) (see Table 1). The concentration of glutamate in the synaptic cleft created by spillover of glutamate from neighboring release sites is calculated by integrating glutamate concentration arising from a single release event at different locations of neighboring release sites scattered from r_{MD} to R_{MF} (Saftenku. 2005). Using the base parameter values, there are approximately 5 neighbors.

Glutamate uptake is handled by an absorbing boundary utilizing the experimentally determined residence time of glutamate in the extracellular space (Trommershauser et al., 1999), which includes the combined effects of transporters located at the glial sheath as well as synaptic uptake (Fig. 1). This technique allows inclusion of transporter effects without requiring the detailed mechanics and kinetics of GLAST (thought to be the main transporter at the glomerulus—see (Overstreet et al., 1999)), which are yet to be determined. The absorbing boundary in the radial direction, r_{abs}, is 2.5–3.5 μm measured from the center of the mossy fiber. The normal or z-direction absorbing boundary (R_{dd}) is equal to the difference between r_{abs} and R_{MF}, which is equivalent to at least the thickness of a single dendritic digit.

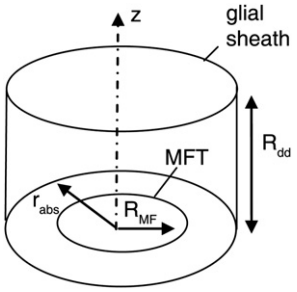

Fig. 1. Saftenku cerebellar glomerulus diffusion model (Saftenku, 2005). Mossy fiber terminal (MFT) is surrounded by a glial sheath. R_{abs} is the radius of the absorbing boundary representing glutamate uptake by the sheath, and R_{dd} is the thickness of a single dendritic digit.

Table 1
Diffusion model parameter definitions, values, and references.

Parameter description	Name	Base value	Physiological range	Reference(s)
Mossy fiber radius (μm)	R_{MF}	1.5	1.5–2	(Hamori et al., 1997; Xu-Friedman and Regehr, 2003)
Distance from center of mossy fiber to glial sheath (μm)	r_{abs}	3.0	$R_{MF}+1.5$	(Xu-Friedman and Regehr, 2003)
Distance from mossy fiber to glial sheath (μm)	R_{dd}	1.5	1–1.5	(Saftenku, 2005)
Radius of circle containing one release site $=\sqrt{\nu_s \pi}$ (μm)	r_{MD}	0.46	0.3–0.46	(Saftenku, 2005 (equation)). See ν_s references (values)
Initial glutamate concentration (mM)	C_0	8.77	4.39–17.54	(Xu-Friedman and Regehr, 2003)
Effective diffusion constant (μm^2/ms)	D_{eff}	0.41	0.41–0.76	(Barbour, 2001; Nicholson and Sykova, 1998; Nielsen et al., 2004; Saftenku, 2005)
Average release site density (μm^{-2})	ν_s	1.5	1.5–3.5	(Rusakov et al., 1999; Sorra and Harris, 1998; Xu-Friedman and Regehr, 2003)
Average radius of post-synaptic density (μm)	a	0.11	0.11	(Xu-Friedman and Regehr, 2003)