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Review

Astrocytes and presynaptic plasticity in the striatum: Evidence and unanswered questions

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ABSTRACT

One of the main functions of astrocytes is to ensure glutamate homeostasis by glutamate uptake and glutamine synthesis. However, during the past ten years it has become clear that astrocytes may also induce changes in synaptic glutamate release when respective pathways must cope with the consequences of brain damage or other alterations in their functional requirements. The loss of glutamatergic synapses in Parkinson's and Huntington's disease is likely to associate with a continuous redistribution of presynaptic activity within the pool of surviving synapses, and astrocytes may have a role in the maintenance of independent control at individual glutamate release sites. The rodent striatum should be a good model structure to analyse astrocyte-synapse interactions underlying disease-related plasticity, because it does not itself contain any glutamatergic neurons. Here we examine recent results that may shed light on the mechanisms underlying pathway-specific alterations in the corticostriatal or thalamostriatal synaptic transmission with a possible involvement of astrocytic release or uptake of glutamate. The conclusions emphasize the need of exploring the highly compartmentalised and presumably heterogeneous synapse astrocyte-interactions at a single synapse level.

Contents

1. Introduction

Presynaptic plasticity is a major mechanism in the control of attention to salient sensory stimuli and goal-directed movements. In the dorsal striatum these functions are implemented by a division of labor between the thalamostriatal and corticostriatal afferent pathways (Smith et al., 2014; Graybiel and Grafton, 2015). Both inputs are glutamatergic, reasonably well preserved in sagittal slice preparations and accessible for direct comparison of optogenetically induced responses (Sciamanna et al., 2015). In line with earlier results from "blind" electrical stimulation of the medial thalamus and motor cortex (Ding et al., 2008), marked differences were found in the release characteristics of thalamo- versus corticostriatal afferents (Ellender et al., 2013; Sciamanna et al., 2015).

Presynaptic plasticity is bidirectional and may include short- and long-term versions of synaptic modification (Atwood et al.,

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2014b; Wu et al., 2015; Korte and Schmitz, 2016). Among the new concepts entering the field of presynaptic plasticity is that three instead of two cellular elements participate in the control of the synaptic release of neurotransmitters (Perea and Araque, 2007; Santello and Volterra, 2009; Wu et al., 2015; Petrelli and Bezzi, 2016; De Pitta and Brunel, 2016; Letellier et al., 2016). Astrocytic signals can either go for the postsynaptic neuron to promote the release of retrograde messengers or bypass the postsynaptic neuron and directly modify exocytosis in the presynaptic terminals (see (Atwood et al., 2014b) for examples). Variability in i) the G-protein-coupled receptor (GPCR) expression, ii) the spatial conditions of gliotransmitter access and iii) the phenotypes of involved astrocytes create a multitude of possibilities for astrocyte-dependent fine-tuning of presynaptic activity and structure.

The striatum is well suited for any study on the relationship(s) between glutamatergic afferents and astrocytes because this region does not contain glutamatergic neurons. Therefore glutamate is either provided by a glutamatergic synaptic terminal or by an astrocyte. The rodent striatum resembles the caudate-putamen of primates in that it mostly contains GABAergic neurons (~99%). The GABAergic striatal projection neurons (SPNs) are specifically committed to either serve movement initiation or movement suppression (Albin et al., 1989). The former function is associated with the activity of dopamine type 1 receptor-(D1R)-expressing SPNs, i.e. SPNs that reach the *s. nigra pars compacta* directly (dSPNs). The latter function is associated with dopamine type 2 receptor-(D2R)-expressing SPNs, i.e. SPNs that connect to the *nigra* indirectly, through the *globus pallidum* (iSPNs). SPNs receive two types of glutamatergic inputs: one originating in the cerebral cortex (Ctx) and another one from the *centrum medianum* and parafascicular nucleus of the medial thalamus (CM/PF). The respective synaptic terminals can be distinguished according to the vesicular glutamate transporters, vGluT1 (Ctx) and vGluT2 (PF). Although one may further distinguish at least two subclasses among the cortical afferent systems, the initially observed diversity of connections originating from distinct cortical layers leveled out when more experimental data accumulated. The differences between CM and PF afferents could, however, be larger than initially assumed (Ellender et al., 2013). The cartoons of Fig. 1A, B show, in a highly simplified manner, the main elements constituting the movement-related pathways through the dorsal striatum. The intrastriatal connections formed by cholinergic and GABAergic interneurons are omitted.

Although current knowledge on the pathway-specific expression of presynaptic receptors must be regarded as incomplete, there are some good reasons to expect that the afferents from the cerebral cortex and the CM/PF process astrocytic signals in a distinct manner (or receive signals from different types of astrocytes). Table 1 summarizes what is currently known about the contrasting features of corticostriatal as opposed to thalamostriatal synaptic transmission. Please note that some of the properties previously ascribed to all thalamostriatal synapses (paired pulse ratio, NMDAR/AMPAR ratio) are now known to reflect properties of the PF rather than the CM input (see Smith et al., 2014). Apart from the use of different transporters for vesicular glutamate uptake (Kupferschmidt and Lovinger, 2015) and different molecular signals needed for synapse formation (Ding et al., 2012), major differences seem to exist in the site of termination (spine vs. dendritic shaft), presynaptic GPCRs signals (no CB1 in thalamostriatal afferents), probability of glutamate release (higher in the PF-STR pathway), the NMDA/AMPA ratio in the postsynaptic response (larger in the CTX-STR pathway) and in the time course of EPSCs (shorter duration in PF-STR connections). Under a system physiology perspective, such differences make sense if one considers that the corticostriatal and the thalamostriatal inputs convey different types of information: the former play a role in motivation-dependent goal-directed behavior while thalamocortical signals are implied in the initiation of attention shifts (Ding et al., 2010).

Fig. 1A, B acknowledges the presence of diverse astroglia as potentially relevant elements in the two glutamatergic pathways of the striatum, but the properties and precise roles of striatal astrocytes in synaptic transmission have only recently become subject of intense studies, mostly for their potential role in Parkinson's disease (PD), Huntington's disease (HD) or other neurological conditions (Beart and O'Shea, 2007; Sheldon and Robinson, 2007; Kim et al., 2011; Pekny et al., 2016; Filous and Silver, 2016). The predominant use of adult mice for single cell studies in HD (Tong et al., 2014; Dvorzhak et al., 2016; Jiang et al., 2016) has helped to avoid some generalizations made from immature or dedifferentiated tissue preparations.

As in other brain regions, the majority of astrocytes in the striatum can be identified by their immunoreactivity (IR) for S100beta and ALDH1l1. About 20% of S100beta-positive striatal astrocytes stain with antibodies against glial fibrillary acidic protein (GFAP) (Vagner et al., 2016), a marker for astrocyte reactivity (Burda and Sofroniew, 2014; Pekny et al., 2016). Due to the availability of a GFAP promoter (gfaABC1D) suitable for packaging into adenoviral vectors (Tong et al., 2014), the subtype of GFAP-positive astrocytes has received increased attention (Dvorzhak et al., 2016; Jiang et al., 2016). However, whether GFAP-positive/"reactive" astrocytes differ from GFAP-negative astrocytes in their ability to control glutamate release remains to be established. At this point it is still "unknown to what extent the reactive astrocyte state is stable, transient, or represents multiple phenotypes" (Zamanian et al., 2012).

In contrast to neurons, transmitter-based classifications of astrocytes are not in use, and it is not known to what extent heterogeneity of gliocrine properties contributes to the diversity of presynaptic effects induced by astrocyte depolarization or receptor-mediated calcium signals. In the following, we apply the term "gliotransmitter" (Parpura and Zorec, 2010; Verkhratsky et al., 2016) in a wider sense, regardless of their modes of release. We shall focus on existing and forthcoming evidence in support of the idea that striatal astrocytes i) differ with respect to the preferentially released gliotransmitter and ii) produce pathway-specific presynaptic modifications of glutamatergic synaptic transmission. This short review can by no means be complete, but we hope that the selected literature and the description of some new findings from our lab will illustrate emerging opportunities (and possibly some drawbacks) connected with the use of optogenetic approaches in addition to the classical electrophysiological and morphological techniques.

2. Evidence for astrocyte diversity and pathway-specific actions of striatal astrocytes

Through their influence on ambient glutamate concentration, striatal astrocytes may enhance the functional impact of a pathway by affecting its efferent elements. Indeed, a groundbreaking publication from the Araque group (Martin et al., 2015) has demonstrated that high-frequency action potential generation in dSPNs induces the release of glutamate from a specific set of astrocytes that act back to dSPNs by activating NMDARs. In contrast, activity of iSPNs stimulates glutamate release from another set of astrocytes that act back to iSPNs, but now via mGluRs. The data suggests that distinct populations of astrocytes are committed to serve the pathway of movement initiation as opposed to the pathway of movement suppression.

More direct evidence in support of astrocyte diversity in the dorsal striatum was obtained by recent experiments in our lab (Dvorzhak, Prigge, Vagner, Wojtowicz and Grantyn, unpublished). The experiments were performed on 15deg off-sagittal slices from

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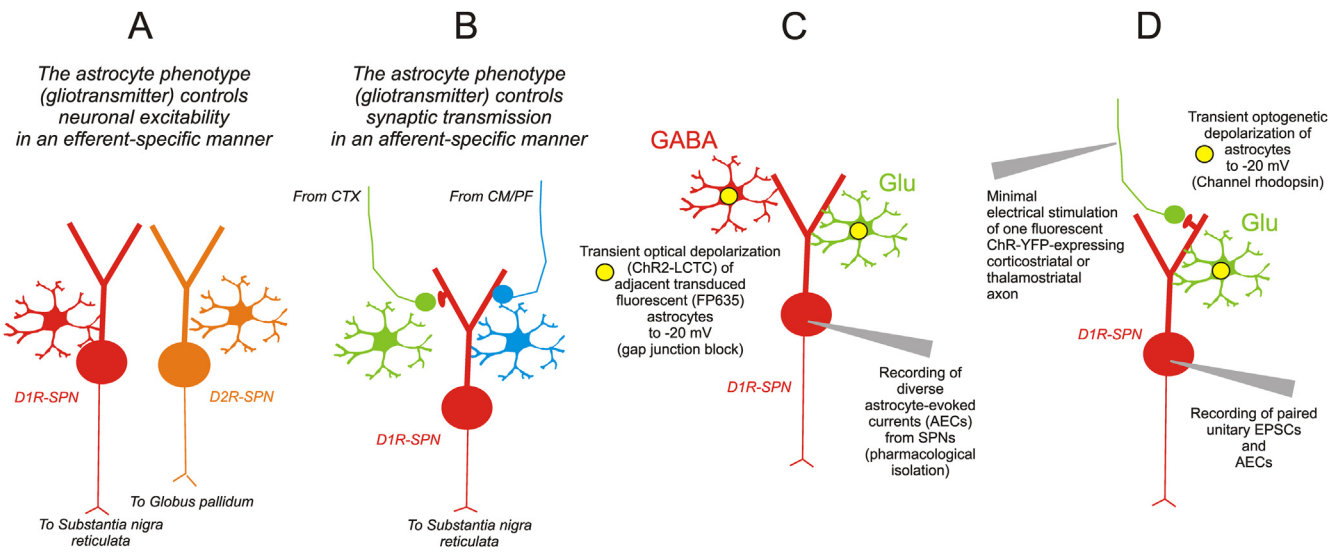

Fig. 1. (A, B) Astrocytes may specialize according to the requirements of the postsynaptic (A) or the presynaptic (B) elements of a pathway. (C, D) Optogenetic approaches may help to test for transmitter-based astrocyte diversity (C), as attempted in Fig. 2, and for afferent-specific astrocytic glutamate effects (D), as attempted in Fig. 3. For comparison of astrocyte actions on thalamostriatal as opposed to corticostriatal connections, the required data is either obtained from different animals injected with the same construct or the same animals, but using a different reporter fluorochrome.

Table 1
Comparison of the two glutamatergic afferent systems to the rodent striatum. Table references (Zheng and Wilson, 2002; Smith et al., 2004; Lacey et al., 2005; Fujiyama et al., 2006; Raju et al., 2006; Moss and Bolam, 2008; Smeal et al., 2008; Mathur et al., 2011; Ding et al., 2012; Ellender et al., 2013; Atwood et al., 2014a; Wu et al., 2015; Sciamanna et al., 2015; Kupferschmidt and Lovinger, 2015; Iskhakova and Smith, 2016).

Parameter	Ctx	Thal (CM/PF)	Refs
Vesicular transporter	vGluT1	vGluT2	Kaneko and Fujiyama, 2002
Semaphorin 3E-dep synaptogenesis	no	yes	Ding et al., 2012
Configuration	stereotyped config.	variable (2 spines etc)	Moss and Bolam, 2008
Spine to shaft contacts in matrix	on spines	half and half	Fujiyama et al., 2006; Raju et al., 2006
Contacts per connection	1	?	Zheng and Wilson, 2002
Location (rev.pot.)	more proximal	more distal	Smeal et al., 2008
Probability of release	low (0.42)	high (0.72)	Ding et al., 2008
Short-term plasticity	PPF	PPD	Ding et al., 2008; Ellender et al., 2013; Sciamanna et al., 2015
LTP	easier		Ding et al., 2008
Presynaptic mGluR1a	no	yes	Smith et al., 2004
Presynaptic mGluR 2/3	yes	yes	Smith et al., 2004; Kupferschmidt and Lovinger, 2015
Presynaptic mGluR4 and 7	yes	yes	Iskhakova and Smith, 2016
NMDA/AMPA ratio	large	small	Ding et al., 2008; Smeal et al., 2008; Ellender et al., 2013
Presynaptic CB1	yes	no	Wu et al., 2015
Serotonin-dep LTD	yes	no	Mathur et al., 2011
Opioid-dep LTD	no	yes	Atwood et al., 2014a,b
Presynaptic GABA(B)	yes	yes	Lacey et al., 2005; Kupferschmidt and Lovinger, 2015

1 year old mice which optimally preserves the glutamatergic connectome of the dorsal striatum. In the experiment of Figs. 1C and 2, two or more different astrocytes were found in functional contact with one (GABAergic) D1R SPN. Using a channel rhodopsin-based optogenetic approach to depolarize individual striatal astrocytes, we moved the stimulating laser beam from one to the next transduced astrocyte and tested the central SPN for the generation of compound astrocyte-evoked currents (AECs). The latter were small (up to 50 pA) but stable in the course of repeated 1/10 s activation which allowed for pharmacological analysis of the AEC components. Interestingly, the size of the GABAergic versus glutamatergic AECs largely differed between the stimulated astrocytes, while the D1-mediated components were similar. Based on our still limited data, i.e. recordings from a total of 11 SPNs with 2 to 4 stimulated astrocytes, we conclude that the diversity of neuronal responses to astrocyte depolarization might be based on the nature of the preferentially released gliotransmitter and/or the availability of respective receptors in the receiving neuron, thereby providing a means to verify the hypothesis of Fig. 1A. With the additional use of BAC reporter mice to discriminate between D1 and D2 SPNs (Gangarossa et al., 2013) one should be able to quantify eventually existing effects on dSPNs vs. iSPNs.

Although potentially useful, the experimental design presented in Figs. 1 C and 2 should not go without discussing some critical questions. First of all: What condition would ever drive an astrocyte's membrane potential up to −20 mV? Recent models (Sibille et al., 2015) and experimental studies in the visual cortex of adult living mice (Enger et al., 2015) predict much smaller K+-dependent depolarization even at high-frequency neuronal activation or spreading depression. But KCl-induced depolarization can combine with an elevation of intracellular Na^+ levels which adds to the reduction of the driving forces for GLT1, the principal glutamate transporter protein in the adult forebrain (Danbolt, 2001; Vandenberg and Ryan, 2013; Jensen et al., 2015). It is quite telling that in epilepsy (Heuser et al., 2010; Hubbard et al., 2016), Huntington's disease (Tong et al., 2014; Dvorzhak et al.,

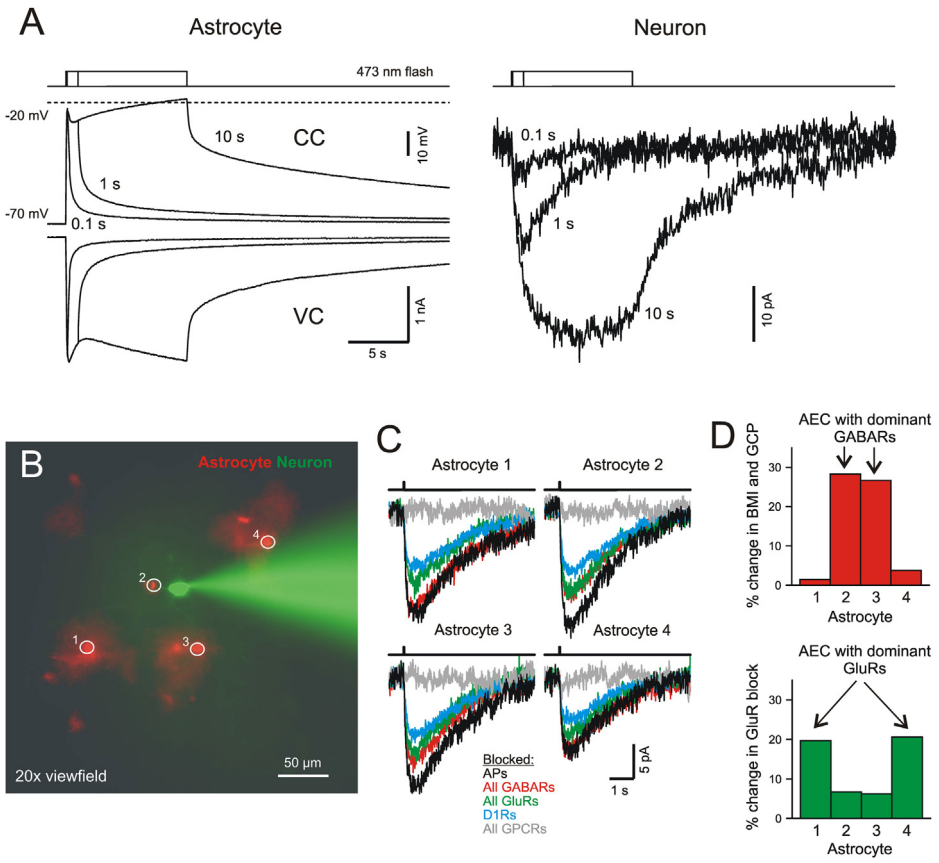

Fig. 2. Channel rhodopsin-induced responses in neighboring astrocytes and neurons (A) and possible diversity of released gliotransmitters in astrocytes converging at the same SPN (B-D). Stereotaxic injection of 1 µl of AAV9-gfaABC1D-ChR2(LCTC)-p2a-FP635 into the dorsal striatum. All tests 3 weeks after injection. (A) Simultaneous recordings from an astrocyte (left) and a neuron (right). CC – current clamp, VC – voltage clamp. Varying the duration of ChR2(LCTC) activation in the astrocyte (upper trace) produced responses of various amplitude (maximal astrocyte depolarization 50 mV). The respective current responses in the neighboring neurons increased with the duration of the light flash to the astrocyte. For comparison of several astrocytic inputs to one neuron, the flash duration was set to 3 ms, and the responses were averaged. (B) Viewfield with a total of 6 different astrocytes. The responses to astrocytes #1–4 are shown. (C) While D1 block produced similar AEC changes (25–35%), there was an inverse pattern of glutamatergic and GABAergic AEC components as isolated by sequential application of respective iGluR and GABA(A)R blockers and quantified in (D).

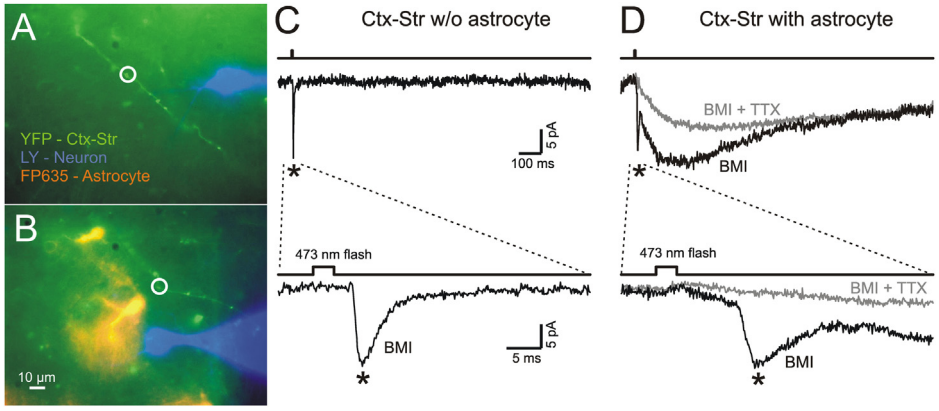

Fig. 3. Experimental configuration to record optically or electrically evoked corticostriatal unitary EPSCs along with AECs. Intrastriatal injection of AAV-gfaABC1D-ChR2(LCTC)-p2a-FP635 and intracortical injection of AAV9/CaMKIIa.hChR2(E123T/T159C)-eYFP.hGH. (A, B) – Overlay images of two different viewfields. Note absence of transduced astrocytes in (A) and presence of a CHR2+ astrocyte next to the recorded D1R+ SPN (injected with Lucifer yellow, LY) in (B). (C) Optical or minimal electrical stimulation of the corticostriatal axon (circle) in (A) produced a unitary EPSC. (D) Combined optical stimulation of a corticostriatal axon (circle) and an astrocyte in (B) produced and EPSC and an additional slow TTX-resistant AEC that could be eliminated by iGluR block.

2016), and perhaps other neurodegenerative diseases (Pekny et al., 2016), deficits in Kir4.1 expression coincide with reduced glutamate uptake and excessive activation of excitotoxicity-promoting extracellular NR2B. In short: while the depolarization applied in the experiments of Figs. 1C and 2 is likely to exceed the activity-dependent astrocyte depolarization, one could expect a much larger drop in the driving forces for GLT1 under pathological conditions – to the extent that glutamate uptake is driven into a reverse mode of function. This approach may then be used to establish a first short list of *possible* mechanisms in the regulation of extrasynaptic and synaptic signal transmission (see Fig. 3 for further applications).

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3. Role of astrocytic gliotransmitters in the control of synaptic glutamate release

Presynaptic astrocyte-dependent modulatory actions in the striatum have been described for inhibitory GABAergic synaptic transmission (Wojtowicz et al., 2013; Dvorzhak et al., 2013). These studies suggested an involvement of presynaptic GABA(B) and CB1 receptors. In excitatory glutamatergic synaptic connections, the most effective synaptic modulator of astrocyte origin is adenosine. To what extent corticostriatal and thalamostriatal afferents differ with regard to the expression of presynaptic adenosine receptors is not well known. (Flagmeyer et al., 1997) found a strong depression of A1 receptors in both corticostriatal and thalamostriatal synaptic transmission but no effect of an exogenous A2 ligand. A2-mediated modifications of synaptic glutamate release have been demonstrated in unitary responses to Schaffer collateral activation (Panatier et al., 2011). In this case, mGluR5-mediated Ca-dependent astrocytic glutamate release produced a potentiation of basal synaptic glutamate release, due to a calcium-dependent release of purines and activation of presynaptic A2a receptors. These receptors can reduce the efficacy of co-localized inhibitory A1 receptors (Ciruela et al., 2006) and modify the effects of other neuromodulators, such as BDNF (Cunha, 2016). It should be noted, however, that in the adult rodent striatum mGluR5 is unlikely to play a prominent role as astrocytic glutamate sensors and mediators of calcium-dependent gliotransmission, because the expression level is rather low (Sun et al., 2013). At least in GFAP-expressing astrocytes mGluR3 is much more abundant than mGluR5 (Jiang et al., 2016).

A particularly intriguing question concerns the role of dopamine (DA) as a potential messenger of astrocyte origin. Optogenetic depolarization of astrocytes resulted in DA release as demonstrated by the sensitivity of dSPNs to D1 receptor block (Fig. 2). D1 and D2 receptors were also found in astrocytes (Vermeulen et al., 1994; Khan et al., 2001). DA produces calcium elevations (Vaarmann et al., 2010) which could enable glutamate release (Parpura and Haydon, 2000). Astrocytes take up L-Dopa from the circulating blood (Inyushin et al., 2012) and regulate extracellular DA levels by means of DA transport proteins (Pelton et al., 1981; Inazu et al., 1999). One can assume that the lack of DA will be sensed by the astrocytes which may then act back to neurons (Jennings and Rusakov, 2016). There is no published evidence yet on dopaminergic astrocyte-synapse interactions, but a recent paper from the Kreitzer group illuminates the experimental approaches currently available to unravel a role of DA in the implementation of pathway-specific synapse alterations (Parker et al., 2016). Parker et al. applied DA deprivation and found that among the 4 possible combinations in the input-output relations of the striatum only PF-dSPN connections changed under the influence of the given DA deficiency protocol. Likewise, MPTP-treated Parkinsonian monkeys were found to exhibit a preferential loss of thalamostriatal over corticostriatal glutamatergic synapses (Villalba et al., 2013).

The highest chance to observe diversity of presynaptic actions is possibly associated with the differential capacity of astrocytes to release glutamate and the presynaptic terminals to express variable mGluR combinations. Glutamatergic terminals in the striatum are, in general, abundantly supplied with mGluR2/3, mGluR4 and mGluR7 (Schwendt et al., 2012; Iskhakova and Smith, 2016). mGluR4, a member of the group III family, was found in 74% of vGluT1 terminals but the abundance of mGluR4-positive glutamatergic terminals was two times higher on iSPN spines than on dSPN spines (Iskhakova and Smith, 2016). mGluR4 has received particular attention for its presynaptic depressant actions on corticostriatal transmission (Pisani et al., 1997) and the relevance of this effect for the treatment of PD and HD (Gubellini et al., 2014). A depressant physiological action of mGluR2/3 has been demonstrated by brain slice photometry using the genetically encoded calcium indicator GCaMP6 expressed in corticostriatal axons (Kupferschmidt and Lovinger, 2015).

Astrocyte-synapse relationships change with neuronal activity (see (Theodosis et al., 2008; Allen, 2013; Gundersen et al., 2015) for more information). But the responsiveness of individual synapses to alterations in their microenvironment and, respectively, their vulnerability under pathological conditions may differ. Using optogenetic hyperpolarization of astrocytes in postnatal hippocampal slices (Letellier et al., 2016) demonstrated that astrocytes can produce a broad spectrum of release characteristics at individual synaptic terminals. This may create a functional disparity between convergent inputs with the possible effect of selective stabilization. Further testing of this interesting hypothesis will require experiments at the level of unitary connections or even at a single synapse level. Recent advancement in the field of glutamate sensors might open new possibilities to evaluate glutamate release with a single terminal resolution (Helassa et al., 2016; Dürst et al., 2016).

A question that can be answered with the presently available tools concerns the time course of astrocytic glutamate signals with respect to corticostriatal (or thalamostriatal) synaptic input to SPNs. Using an optogenetic approach to induce the release of glutamate from single astrocytes in combination with the stimulation of single corticostriatal axons (see Fig. 1D for a scheme of experiment) we recorded the respective AECs and EPSCs (Dvorzhak, Vagner, Grantyn, unpublished). Fig. 3 shows that in a single-pulse paradigm the EPSCs and AECs exhibited little overlap, but the time difference between the EPSC and AEC peaks was only 180–200 ms. Under condition of repetitive activation the presynaptic terminals would be exposed to sizeable amounts of astrocytic glutamate (and other "gliotransmitters"), but further experiments are needed to find out whether release sites of cortical as opposed to thalamic origin were modulated in a differential manner.

4. A contribution of astrocytic glutamate uptake to the control of synaptic glutamate release?

The efficacy of glutamate as a neurotransmitter at excitatory synapses relies on the rapid switch between states of very high (up to 3 mM (Raghavachari and Lisman, 2004; Greget et al., 2011; Kessler, 2013)) and very low (25 nM (Herman and Jahr, 2007)) glutamate concentration. The maintenance of very low extracellular glutamate levels is crucial for the maintenance of neurons and synapses in a healthy functional state. Four types of high-affinity electrogenic transporters, two neutral amino acid transporters and several splice variants, are available in the mammalian brain for removal of glutamate from the extracellular space (Danbolt, 2001; Vandenberg and Ryan, 2013; Jensen et al., 2015). The bigger part of this job is performed by EAAT2 (GLT1 in rodents), the most abundant glutamate transporter in adult striatal astrocytes (Rothstein et al., 1996) where glutamate uptake not only accounts for the efficient clearance of the neurotransmitter from extracellular space but also for the initiation of the glutamate-glutamine cycle to replenish the glutamate reserve in presynaptic terminals.

EAAT2 is a strongly electrogenic transporter. According to its stoichiometry, each transport cycle moves 1 Glu^-, 3 Na^+ and 1 H^+ into the cell, and 1 K^+ out of the cell (Vandenberg and Ryan, 2013; Grewer et al., 2014). Conditions producing depolarization and high extracellular [K^+] will reduce the efficacy of glutamate uptake, thereby impeding transmitter clearance from the extracellular space. The described neuronal reactions to inefficient glutamate

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clearance range from enhanced activity of extrasynaptic NMDAR (Shen et al., 2014; Armbruster et al., 2016) and/or group I mGluR (Molinari et al., 2012; Hauser et al., 2013) to changes in respective forms of synaptic plasticity (Tzingounis and Wadiche, 2007). However, there is a high degree of variability in the astrocyte-synapse configurations, which suggests the existence of different degrees of spillover and synaptic clearance at different types of terminals. Thus, astrocyte-synapse interactions must be determined for any given type of connection.

The cellular and synaptic consequences of reduced glutamate uptake have been studied by partial block of GLT1 with TBOA, conditional knockout of *SLC1A2* and by using mouse lines with disease-related GLT1 deficiency (see (Tzingounis and Wadiche, 2007) for a review of earlier literature). The results are controversial. It seems quite possible that in the healthy brain glutamate uptake operates with a sufficient functional reserve, i.e. it is hardly overwhelmed even under conditions of high-frequency activation of synaptic inputs (Diamond and Jahr, 2000). At the single synapse level, Jahr and colleagues observed no changes in the time course of glutamate transporter currents (GTCs) when the transport was exposed to partial pharmacological block (Wadiche et al., 2006). More recently, however, (Armbruster et al., 2016) provided iGluSnFR-based evidence from the adult cerebral cortex showing that enhanced presynaptic neuronal activity rapidly and reversibly slows glutamate clearance if the frequency of intracortical stimulation exceeds 30/s. The absolute amount of released glutamate appears to be irrelevant. As for the striatum, a role of astroglial glutamate uptake was first demonstrated for corticostriatal synaptic transmission (Goubard et al., 2011). Graded pharmacological blocking of astrocytic glutamate uptake produced a desensitization of AMPA receptors. (Beurrier et al., 2009) reported a TBOA-induced prolongation of EPSCs generated at frequencies >50/s.

Studies on the rodent (Minelli et al., 2001) and human cerebral cortex (Melone et al., 2011) showed that the GLT1 immunoreactivity (IR) is not evenly distributed but forms clusters adjacent to the areas of presynaptic vesicle accumulation. The impact of GLT1 would then largely depend on the number of transporter molecules at synaptic sites, a variable influenced by cAMP-mediated vesicular replenishment of transporter aggregates (Li et al., 2015). As an active constituent of a tripartite synapse array (Araque et al., 1999; Perea and Araque, 2007), the glutamate transporter clusters are presumed to facilitate or to depress synaptic transmission. How this is achieved at any given type of synapse is now slowly being discovered, first of all due to research on animal models of disease where glutamate uptake is deficient but able to recover. Animal models of disease may thus offer an opportunity for contrastive testing.

There is little doubt that the gene encoding GLT1 (*SLC1A2*) is downregulated in HD (Lievens et al., 2001; Behrens et al., 2002; Shin et al., 2005; Miller et al., 2008; Faideau et al., 2010; Huang et al., 2010; Menalled et al., 2012; Grewer et al., 2014; Langfelder et al., 2016; Meunier et al., 2016). Mouse models of HD were therefore studied to determine the causes and consequences of presumably impaired glutamate transport. First of all, by applying exogenous glutamate or aspartate it was confirmed that the down-regulation of *SLC1A2* in HD mice indeed resulted in a decreased tissue uptake (Lievens et al., 2001; Behrens et al., 2002; Shin et al., 2005; Miller et al., 2008; Faideau et al., 2010; Huang et al., 2010; Grewer et al., 2014). An HD-related slowing of glutamate clearance was also found after synaptic activation (Jiang et al., 2016). In this case the glutamate sensor iGluSnFR was expressed in astrocytes. Another study, with iGluSnFR expression in SPNs, failed to reveal HD-related differences after intrastriatal electrical stimulation (Parsons et al., 2016). (Dvorzhak et al., 2016) recorded the glutamate-induced intracellular [Na^+] transients of single SBFI-loaded astrocytes and observed a significant HD-related reduction of glutamate transport in sulphorhodamine-labelled astrocytes, but not in astrocytes expressing Tomato under a GFAP promoter. The latter result (Dvorzhak and Grantyn, unpublished) hints a differential vulnerability of glutamate uptake in different types of astrocytes.

Considering the controversial character of previous findings and the high degree of compartmentalization in the astrocyte-synapse interactions, it is necessary to collect more material from individual glutamatergic synapses. As a step into that direction, we have examined the decay of glutamate-induced spine currents (GISCs) and found significantly increased time constants of decay and lower GISC amplitudes when glutamate uptake was weakened by Ba^{2+}-induced depolarization (Fig. 4).

Single synapse data documenting presynaptic effects of deficient astrocytic glutamate uptake are not yet available. However, experiments with a new adult conditional GLT1 knockout mouse (GLASTCreERT2/+/GLT1flox/flox) revealed an increase in the mean amplitude and the paired pulse ratio of glutamatergic EPSCs under condition of repetitive electrical stimulation (Aida et al., 2015). This result suggests that elevation of the perisynaptic glutamate concentration may activate a release-promoting messenger with the consequence that a larger fraction of the readily releasable pool is released with the first stimulus. Analyzing unitary corticostriatal EPSCs (as shown in Fig. 3C), we found evidence in support of the Aida et al. study, i.e. HD mice indeed generated larger mean unitary EPSC amplitudes, and this was associated with a significantly decreased failure rate (Dvorzhak, Wojtowicz, Melnick, Grantyn, unpublished).

The idea of release facilitation in individual corticostriatal synapses with deficient glutamate uptake would however be at variance with the prevailing viewpoint that *"the field has moved from thinking that striatal pathology in HD was driven by excitotoxic mechanisms to the view that, if anything, it is a hypoexcitability disorder driven by impaired corticostriatal signaling"* (Plotkin and Surmeier, 2015). Synapse counts in Q140 hets (Deng et al., 2013) and Q175 homs (Rothe et al., 2015) showed lower than in WT densities of vGluT1-IR terminals. Several labs reported a respective decrease in the spine density of HD mice in the striatum. Finally, it was shown that the amplitude range of unitary corticostriatal EPSCs decreased which may reflect an HD-related reduction in the number of maximally available synaptic sites in the still functional connections (Rothe et al., 2015).

The discrepancy between the possible potentiation of single glutamate release sites and the overall decrease in the number of glutamatergic synapses under condition of deficient glutamate uptake raises further questions on the significance of glutamate clearance for the maintenance of synaptic contacts. At this point it is not known whether downscaling of the corticostriatal and/or thalamostriatal input is actually under the influence of the reduced GLT1 expression or, on the contrary, GLT1 is downregulated because fewer release sites require fewer GLT1 clusters. As for the reverse direction, i.e. signal flow from astrocyte to synapse, it has been shown that the conditional knockout of GLT1 at day E19 (Aida et al., 2015) has produced a slight decrease in PSD95 protein 4 weeks post tamoxifen injection, but the n was too small to reach significance. As for the direct direction, from synapse to astrocyte, it was shown that the knockout of vGluT1 (only possible at early postnatal age) produced substantial changes in the size and complexity of astrocytic domains in the cerebral cortex (Morel et al., 2014) which may have consequences for the number and distribution of glutamate transporter sites. Co-culture experiments showed that the presence of glutamatergic synapses fostered the expression of GLT1 and GLAST in rat cortical astrocytes (Swanson et al., 1997). Regional de-afferentation experiments performed in var-

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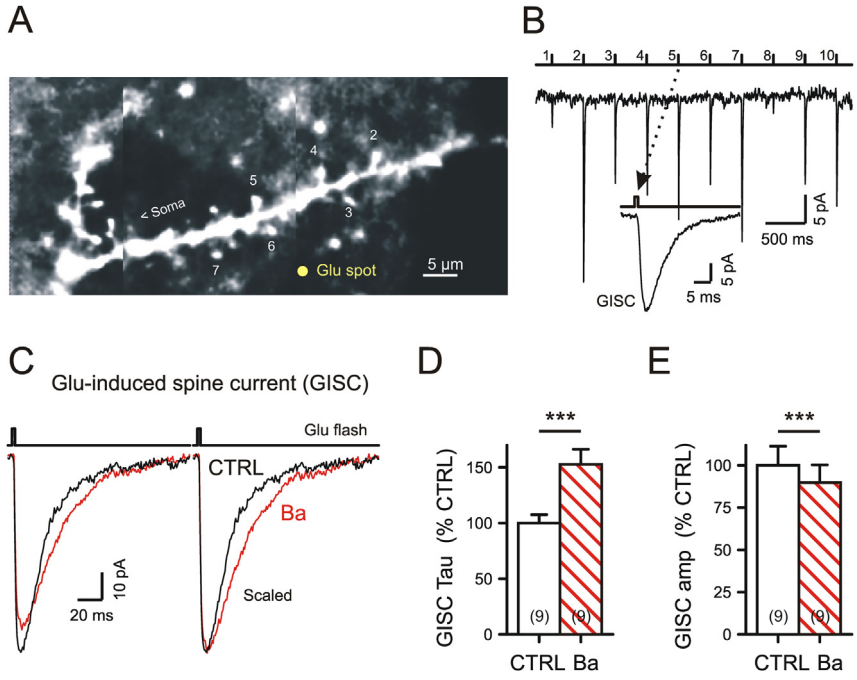

Fig. 4. Impairment of astrocytic glutamate uptake by membrane depolarization with Ba^{2+} results in slowing of glutamate-induced single spine currents in WT SPNs. (A) Single spines were visualized by filling SPNs with Alexa Fluor 568 hydrazide. For these experiments we chose dendrites running in parallel with the slice surface. Appropriate spine images were obtained by deconvolution of z-stacks comprising 100 wide-field 63 x images. (B) Series of GISCs elicited by stimulating different spines, as indicated in (A). The flash duration was adjusted to produce a response mimicking the amplitude of unitary EPSC in SPNs (Rothe et al., 2015). [Rubi-Glu] 1 mM. Pulse duration 1 ms. Laser intensity 3 mW. Presumed spot size ~1 µm. (C) Specimen traces of a WT GISC in CTRL (black) and in Ba2+ (red). On the right – same, but scaled to the current maximum. Experiment in the presence of cyclothiazide (50 µM) and in the absence of added NMDAR blocker (but presence of 1 µM of MK801 in the slice recovery solution). (D, E) Significant effects of Ba2+ (200 µM) on the GISC time constants of decay (GISC Tau) and amplitudes in WT SPNs. Statistics: (B) 2-way RM-stacked-ANOVA. Genotype – $F(1, 30) = 5.73$, $p = 0.023$. Stim int – $F(6, 180) = 3.75$, $p = 0.0015$. (F, G) Paired *t*-tests. Modified from (Dvorzhak et al., 2016).

ious brain regions suggested that the level of GLT1 expression depends on the density of glutamatergic innervation (Ginsberg et al., 1995).

5. Conclusion and prospect

On theoretical grounds, corticostriatal and thalamostriatal synapses may react to changes in astrocytic glutamate release/uptake in a differential manner. To what extent diversity of astrocytes contributes to the diversity of presynaptic modifications still needs to be studied. Of special interest is the upcoming evidence suggesting that the level of astrocytic glutamate release/uptake may influence the efficacy of glutamatergic synaptic transmission on a long-term scale. In the case of disease, the total amount of GLT1 protein might suffice to supply the reduced number of glutamatergic synapses but, at an individual synapse level, there could be mismatches between the presynaptic release capacity and the astrocytic glutamate uptake. Our current hypothesis is that in a set of 3–5 synapses, as typically contained in a unitary corticostriatal connection, the contacts with more pronounced release-uptake mismatch might be at a higher risk of pruning. Thus, with the progression of HD or other neurodegenerative diseases synaptic connections may have to adapt to a decreasing number of contacts by repeated shifts in the position of high-release terminals. Such a scenario would perhaps reconcile the previously prevailing "excitotoxicity hypothesis" with the present "synaptic uncoupling" ideas in the HD literature.

The main task is, of course, to prevent the loss of glutamatergic synapses in neurodegenerative disease. Preclinical studies with intravenous injection of highly blood brain barrier-permeable viral constructs (Deverman et al., 2016) or small molecule therapy with activators of GLT1 transcription (Rothstein et al., 2005; Sari et al., 2010) may help to identify the most critical mechanism leading to synapse loss.

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