Alteration of sensory-evoked metabolic and oscillatory activities in the olfactory bulb of GLAST-deficient mice

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INTRODUCTION

Astrocytes are key cellular elements in both the tripartite synapse and the neurovascular unit. To fulfill this dual role in synaptic activity and metabolism, they express a panel of receptors and transporters that sense glutamate. Among them, the GLT-1 and GLAST transporters are known to regulate extracellular glutamate concentrations at excitatory synapses and consequently modulate glutamate receptor signaling. These major uptake systems are also involved in energy supply to neurons. However, the functional role of GLAST in concurrent regulation of metabolic and neuronal activity is currently unknown.

We took advantage of the attractive structural and functional features of the main olfactory bulb to explore the impact of GLAST on sensory information processing while probing both glutamate uptake and neuronal activity in glomeruli and deeper cellular layers, respectively. Using odor-evoked 2-deoxyglucose imaging and local field potential recordings in GLAST knockout mice, we show in vivo that deletion of GLAST alters both glucose uptake and neuronal oscillations in olfactory bulb networks.

Keywords: glutamate transporters, olfactory bulb, astrocytes, metabolic activity, neuronal oscillations

INTRODUCTION

Astrocytes are structurally positioned to regulate synaptic transmission and neurovascular coupling: they extend perisynaptic processes that cover thousands of synapses and endfeet that are apposed to the blood vessel wall (Haydon and Carmignoto, 2006). An increasing number of studies have established their role in the regulation of energy metabolism (Pellerin, 2008), blood flow (Gordon et al., 2008), and synaptic activity (Fellin, 2009). To fulfill this triple role, astrocytes express a repertoire of transporters and receptors to mediate an active molecular crosstalk with neurons. Among them, glutamate transporters (GlTs) GLAST (for GLutamate–ASpartate T ransporter, EAA T-1) and GLT-1 (for GLutamate T ransporter, EAAT-1) are exclusively expressed by astrocytes and are present at high densities near excitatory synapses (Danbolt, 2001). These transporters prevent excessive accumulation of glutamate and tightly regulate glutamate receptor occupancy and signaling (Huang and Bergles, 2004; Attwell and Ibbot, 2005). GLAST is the major transporter expressed during development, but little is known of its functional roles in adult tissues in vivo. GLT-1 accounts for the majority of glutamate uptake in the adult forebrain (Reith et al., 1994, Ullersvang et al., 1997), but GLAST might be an important contributor in specific pathways.

An advantageous model to study possible roles of GLAST in both metabolic and neuronal activity is the main olfactory bulb (OB), where this transporter is highly expressed in the adult OB (Ussami et al., 2001). Olfactory glomeruli support the initial stage of odor processing. These discrete spherical structures contain synapses between the olfactory receptor neurons (ORN) and the mitral/tufted cells (M/TCs) and receive convergent inputs from ORNs expressing the same odorant receptor (Mombaerts et al., 1996). In deeper layers, M/TCs are modulated by interneurons (granule cells, GCs) through reciprocal dendrodendritic synapses contained in the external plexiform layer (EPL; Rall and Shepherd, 1968). Astrocytes are not homogeneously distributed in the OB, the highest density of GFAP immunoreactivity is found in the glomerular layer (GL) followed by the EPL (Batch and Shipley, 1993). Therefore, both GL and EPL represent key functional units for in vivo studies of the role of neuron-astrocyte interactions in the OB network.

In these two sets of synapses, both spatial and temporal activities that accompany odor processing have been identified. Spatially, odors elicit distributed maps of activated glomeruli (Kauer and White, 2001), first identified using radiolabeled [14C]-2-deoxyglucose (2DG; Johnson et al., 2002). Temporally, neuronal oscillations are prominent in the local field potential (LFP) recorded in the OB (Kay et al., 2009). Since oscillatory rhythms reflect relevant synchronous activities between elements of neural assemblies, they are a good sensor of the functional state of a network (Singer, 1993; Uhlhaas et al., 2009). Information regarding the role of astrocytic GlTs in these two types of activity is still lacking. In the present study we therefore asked whether GLAST activity could alter spatial maps and neuronal oscillations in vivo.
Animals were adult mice (2–8 months) obtained from C57BL/6. Membranes were incubated overnight at 4°C in 25 mM TRIS, pH 7.4, 150 mM NaCl, and 0.1% TWEEN-20 (TBST) and transferred onto nitrocellulose membranes. Membranes were subjected to SDS-PAGE (4% stacking and 12% running gels) and transferred by electroblotting. Membranes were blocked and incubated overnight and then cryoprotected by incubation in a 30% glucose buffer [50 mM TRIS–HCl, pH 7.4, 100 mM NaCl, 1% SDS, protease inhibitor cocktail (1:200, Roche, Basel, Switzerland)]. Total protein content was determined with the BCA Protein Assay Reagent (Thermo Scientific, Waltham, MA, USA). Following an overdose of sodium pentobarbital, one GLAST knockout (GLAST+/−) and one wild-type (GLAST+/+) mouse were killed in succession. Brains were then rapidly removed and frozen in isopentane at −40°C. Coronal sections (100 μm) were obtained using a cryomicrotome, mounted on slide, and analyzed with confocal microscopy (LSM 510, Zeiss, Le Pecq, France). The sections were mounted in FluorSave reagent (Calbiochem, Merck, Darmstadt, Germany), covered with a coverslip associated with a confocal microscope (LSM 510, Zeiss, Le Pecq, France). The sections were mounted in FluorSave reagent (Calbiochem, Merck, Darmstadt, Germany), covered with a coverslip and visualized with confocal microscopy (LSM 510, Carl Zeiss, Oberkochen, Germany). Three distinct areas of the OB were visualized: the granular area (including mitral, internal plexiform, and GC layers), (2) EPL, and (3) GL. Sections were analyzed using the MCID Analysis, associated with a confocal microscope (LSM 510, Carl Zeiss, Oberkochen, Germany). Three distinct areas of the OB were visualized: the granular area (including mitral, internal plexiform, and GC layers), (2) EPL, and (3) GL. 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We used two odorants with different vapor pressures for stimulation delivered. Separated by 1 min intervals during which a constant airflow rate of odorized air in front of the animal’s nose. The protocol for Scientific, Berkeley, USA) that ensured the delivery of a constant and placed into a modified perfusion system (Valvebank AutoMate Technologies, West Warwick, RI, USA), filtered (0.3–300 Hz), digitized at 2 kHz using a CED Power1401 converter (Cambridge Electronic Design, Cambridge, UK), and stored for off-line analysis.

**Odor stimulation**

We used two odorants with different vapor pressures for stimulation: benzaldehyde and hexanal (Sigma-Aldrich; theoretical VP at 25°C 0.975 and 10.9 for benzaldehyde and hexanal, respectively, indicating that hexanal is more volatile than benzaldehyde; Lowery and Kay, 2007). Pure molecular compounds were diluted in mineral oil. Filter papers were loaded with 20 μl of diluted solutions and placed into a modified perfusion system (Valvebank AutoMate Scientific, Berkeley, USA) that ensured the delivery of a constant rate of odorized air in front of the animal’s nose. The protocol for odor stimulation consisted in sets of 10 trials of 5 s odor delivery separated by 1 min intervals during which a constant airflow was delivered.

**LOCAL FIELD POTENTIAL ANALYSIS**

Data were inspected individually to discard trials containing artifacts. Signal analysis was performed off-line with Spike 2 software (Cambridge Electronic Design, Cambridge, UK) and OpenElectrophy software (http://neuralensemble.org/trac/OpenElectrophy; Garcia and Fourcaud-Trocmé, 2009).

Two distinct temporal periods were determined for analysis. During the odor stimulation period (5 s duration), only peaks ranging from 1 to 5 s after the odor onset marker were considered for the analysis, to prevent variability related to odor presentaon and/or sniffing behavior of the animal. The pre-odor period started 8 s prior to odor onset and lasted for 4 s (from –8 to –4 s). Spontaneous activity was analyzed for 5 s before onset of the odor period (from –8 to –3 s). Power spectra were estimated in Spike 2 software using a Fast Fourier transform of LFPs with a Hanning window of 2048 points, which led to a frequency resolution of 0.9766 Hz at the sampling frequency of 2000 Hz. For time–frequency analysis, a wavelet transform was applied to each trial using a family of complex Morlet wavelets, resulting in an estimate of oscillatory power at each time sample and at each frequency between 1 and 160 Hz. This transformation leads (for each trial) to a time–frequency matrix where each point represents the level of energy for a given instant and a given frequency, with hot color spots representing transitory oscillaons. The detection of non-stationary oscillaons in LFPs by OpenElectrophy is based on a method described by Roux et al. (2007) and previously applied to signals recorded in the olfac- tory system by Chapuis et al. (2009). It uses the scalogram to extract individual oscillaons with a ridge extraction method. This method is useful when signals have oscillaons in different frequency bands, when oscillaon frequencies shift as a function of time or when there is no a priori knowledge of the signal.

**ODOR RELATED ACTIVITY IN THE GAMMA (60–160 Hz) AND BETA (15–35 Hz) RANGES**

The same analysis as for spontaneous activity was performed in the gamma range, but in both pre-odor (–8 to –4 s) and odor (1–5 s) periods. In addition, mean power of the time–frequency windows used for peak extraction was compared (before and after odor onset). For analysis of beta activity, the power threshold (mean + 2 STD) was calculated between 15 and 35 Hz during the baseline period ranging from –8 to –4 s before odor onset. Burst detection was performed above this threshold, to determine their energy, precise temporal posi- tion, and instantaneous frequency. Only bursts presenting at least four oscillatory cycles were considered as relevant and kept for analysis.

For each single trial, maximal power values were averaged on all the peaks detected during the time–frequency window, so that we obtained one value per trial. Mean values were then normal- ized relative to the mean power of the time–frequency window corresponding to the same time range and spanning the frequency spectrum between 1 and 160 Hz.

**ANALYSIS OF ELECTRICAL STIMULATIONS**

Averaged evoked potentials were analyzed off-line using Spike 2 software. Blocks of 20 traces were averaged per condition, and...
amplitude, latency, and duration of the peaks and troughs were measured. Significant differences in values were assessed using Student’s t-tests.

RESULTS

GLAST EXPRESSION IN THE OLFACTORY BULB IN ADULT MICE

Consistently with previous published data (Utsumi et al., 2001), GLAST immunofluorescence was observed throughout the OB, with relatively stronger expression in the GL followed by the M/TGs layer and EPL (Figure 1A).

NO OVEREXPRESSION OF GLT-1 IN THE OLFACTORY BULB OF GLAST−/− ADULT MICE

The relative level of expression of GLAST and GLT-1 was measured by immunoblotting of isolated OBs from paired GLAST+/+ and GLAST−/− mice (n = 5 for each; Figure 1B). GluTs antibodies detected distinct proteins in tissue homogenates with molecular weights of ~66 kDa for both GLAST and GLT-1. To ensure comparable protein levels each blot was probed for actin and results normalized against actin. The absence of immunoreactive bands for GLAST confirmed the phenotype of GLAST−/− mice. Semi-quantitative evaluation of the relative levels of GLT-1 expression confirmed the absence of overexpression of this GluT in GLAST−/− mice.

NO BROAD ANATOMICAL CHANGES IN GLAST-KO MICE

GLAST is present on radial glial cells, which guide migrating neurons in the rostral migratory stream to bring new cells into the OB (Díaz et al., 2011), the volumes of the granular area, EPL, and GL were determined from Nissl-stained sections.

FIGURE 1 | Expression of GLAST transporter in the olfactory bulb. (A) Representative section of the adult main olfactory bulb (OB) showing immunolabeling of GLAST in (a) glomerular layer (GL), (b) external plexiform layer (EPL), and (c) mitral/tufted cells and granular cells layers (M/T-GCL). (B) No overexpression of GLT-1 transporter in the OB of GLAST−/− mice. Immunoblot for GLAST (top) and GLT-1 (bottom) in the OB of GLAST+/+ and GLAST−/− mice. As seen on the bar graph, the average relative level of expression of GLT-1 is not different between GLAST+/+ (n = 5) and GLAST−/− (n = 5) mice.

REDUCED METABOLIC RESPONSE TO ODOR STIMULATION IN THE OLFACTORY GLOMERULI OF GLAST−/− MICE

[14C]-2-deoxyglucose studies were performed simultaneously on paired adult GLAST+/+ and GLAST−/− littermates (n = 11 each). Odorant stimulation resulted in a significant increase in 2DG uptake in focal and specific regions of the GL (Figure 2A) as previously shown by numerous studies in the OB (Johnson et al., 2002; see also http://gara.bio.uci.edu/). A region was considered activated when the increase in 2DG uptake spanned the size of a glomerulus (120–160 μm) corresponding to six to eight consecutive coronal sections. We observed that GLAST+/+ and GLAST−/− mice displayed similar spatial olfactory maps after a 2% benzaldehyde stimulation. Activated glomeruli were located in the caudal half of the OB, and on the lateral and medial parts of the structure. Activation on the lateral border of the OB was very reproducible across individuals, so we focused on this region for quantitative analyses (Figure 2A). To compare the specific 2DG uptake between the two strains of mice, we calculated for each section the normalized odor specific activations as the value of 2DG uptake in the region of interest (glomerular region) divided by the basal 2DG uptake measured in the whole section. We compared this odor specific activations as the value of 2DG uptake in the region of interest between GLAST+/+ and GLAST−/− mice, respectively. As shown in Figure 2B, the ratio of 2DG uptake in the region of interest showed a significant difference between the two strains of mice.

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We first compared electrophysiological activity in the absence of the respiratory rhythm was the same in GLAST mice compared to control animals. In the representative digitized autoregressive, grey scale illustrates the level of 2DG uptake for one animal of each genotype (left: GLAST; right: GLAST) and for four consecutive slices of 20 μm thickness. Activated glomerular regions are the black areas at the periphery of the structure (arrows). (B) Relative 2DG uptake averaged for all the animals (GLAST = 11); GLAST = 11) shows that odor-evoked increase in 2DG uptake was significantly reduced in GLAST mice. As displayed on Figure 4D, we found that gamma activity decreased in control mice by 20.2% for benzaldehyde (10.9% increase) and 25.1% for hexanal (16.2% increase) compared to GLAST and GLAST mice. Odor presentation had two opposite effects on the LFP signal: (1) a decrease in gamma frequency range, (2) an appearance of bursts in a lower frequency range (15–35 Hz) that will be referred to as beta burst activity. Figure 4, right panel, frequency decreased with regards to their power and frequency. Next, we analyzed whether modifications also occurred in these mice during odor stimulation.

Gamma-Beta Shift During Odor Stimulation is Changed in GLAST Mice

Odor stimulation was carried out using two chemically distinct odorants, either a low (benzaldehyde: 0.975 μg/ml) or a high vapor pressure (hexanal: 10.9 μg/ml). Odor presentation had two opposite effects on the LFP signal: (1) a decrease in gamma frequency range, (2) an appearance of bursts in a lower frequency range (15–35 Hz) that will be referred to as beta burst activity (Figures 3A,B). In GLAST mice, odor onset triggered an increase in beta oscillations bursts at around 15 Hz, concurrent with the suppression of ongoing high gamma activity for the duration of the stimulation (Figure 4B). Some lower frequency gamma bursts (80–100 Hz) remained during odor stimulation. This clear frequency balance between gamma and beta oscillations was not present in GLAST mice during odor stimulation.

We further estimated the overall power variation of gamma oscillations in a 60–160 Hz frequency band. We compared the average value of time–frequency plots corresponding to the odor stimulation period (from 1 to 5 s after odor onset) with the pre-odor period (from 8 to 4 s prior to odor onset; GLAST mice (n = 4); GLAST mice (n = 4)). As displayed on Figure 4D, we found that gamma power decreased in control mice by 20.2% for hexanal and 25.1% for benzaldehyde. In contrast, no significant decrease was observed in GLAST mice (0.2% and 5.7% for benzaldehyde and hexanal, respectively (GLAST vs. GLAST, F(1,135) = 5.872, p < 0.05). As displayed on Figure 4D, we found that gamma activity decreased in control mice by 20.2% for hexanal and 25.1% for benzaldehyde. In contrast, no significant decrease was observed in GLAST mice (0.2% and 5.7% for benzaldehyde and hexanal, respectively (GLAST vs. GLAST, F(1,135) = 5.872, p < 0.05). As displayed on Figure 4D, we found that gamma activity decreased in control mice by 20.2% for hexanal and 25.1% for benzaldehyde. In contrast, no significant decrease was observed in GLAST mice (0.2% and 5.7% for benzaldehyde and hexanal, respectively (GLAST vs. GLAST, F(1,135) = 5.872, p < 0.05).
FIGURE 3 | Gamma activity recorded during spontaneous activity in the olfactory bulb of GLAST\(^+\)\(^+\) and GLAST\(^-\)\(^-\) mice. (A) Gamma bursts are present on each respiratory cycle, both in a GLAST\(^+\)\(^+\) mouse (left) and a GLAST\(^-\)\(^-\) mouse (right) as displayed on representative local field potential recording examples. Top: raw signals 0.3–300 Hz; bottom: filtered signals 60–160 Hz. (B) Shift of gamma bursts frequency in GLAST\(^-\)\(^-\) mice. The signal is represented as a time (x-axis)–frequency (y-axis) decomposition between 10 and 160 Hz. The color scale represents signal power (\(\mu\text{V}^2\)). (C) Normalized average power spectra 60–160 Hz during spontaneous activity in GLAST\(^+\)\(^+\) \((n = 6)\) and GLAST\(^-\)\(^-\) \((n = 6)\) mice. Frequency and power of gamma oscillations are significantly reduced in GLAST\(^-\)\(^-\) compared to controls. (D) Peak values averaged for the population GLAST\(^+\)\(^+\) \((n = 6)\); GLAST\(^-\)\(^-\) \((n = 6)\) confirm the frequency shift and power decrease in GLAST\(^-\)\(^-\) animals. **\(p < 0.001\).
FIGURE 4 | Effects of odor stimulation on beta (15–35 Hz) and gamma (60–160 Hz) oscillations in GLAST$^{+/+}$ and GLAST$^{-/-}$ mice. 

(A) Representative single trial showing the switch of oscillations during odor presentation (vertical bar, hexanal 2%) in a GLAST$^{+/+}$ (left column) and GLAST$^{-/-}$ (right column) mice. Top traces: beta (15–35 Hz) filtered; bottom traces: gamma (60–160 Hz) filtered LFPs. 

(B) Signal represented for one mouse from each group as a time (x-axis)–frequency (y-axis) decomposition between 2 and 35 Hz (beta band, bottom) and 60–160 Hz (gamma band, top) after processing of raw signals shown in (A). The four plots are set to the same scale for power (color bar). White vertical lines indicate odor onset. 

(C) Individual peaks extracted in the gamma band (60–160 Hz) during pre-odor (from –8 to –4 s; hyphen) and odor period (from 1 to 5 s) under benzaldehyde (diamonds) or hexanal (empty squares) are plotted as function of their power (x-axis) and frequency (y-axis). The frequency shift is clear for both genotypes during odor sampling even though frequency is slower in GLAST$^{-/-}$ mice. Peaks have a lower frequency under benzaldehyde than under hexanal in GLAST$^{+/+}$, no difference in repetition is observed for GLAST$^{-/-}$ mice. 

(D) Decrease in high gamma band (60–160 Hz) power illustrated as the variation (in %) of the average power value comparing the two time–frequency plots (pre-odor from –8 to –4 s) and odor periods (1–5 s) for hexanal 2% (black bars) and benzaldehyde 2% (gray bars). No gamma decrease is observed in GLAST$^{-/-}$ ($n=4$) compared to GLAST$^{+/+}$ ($n=4$) mice. 

(E) Values of beta peaks power for both odors (hexanal 2% in black and benzaldehyde 2% in gray bars) in GLAST$^{+/+}$ and GLAST$^{-/-}$. Power of the peaks is significantly lower in GLAST$^{-/-}$ mice.
hexanal [odor effect F(1,124) = 13.861, p < 0.001]. In GLAST−/− mice (Figure 4C, right panel) frequency decrease was weaker but still present (from 104 to 99 Hz), with no difference between the two odorants [F(1,92) = 0.025, p = 0.87]. As expected from the overall decrease of gamma power (Figure 4D), GLAST+/+ mice displayed a stronger decrease of peaks power than GLAST−/− (interaction power × strain F(1,216) = 28.492, p < 0.0001), and showed a significant difference between odors [ odor effect F(1,92) = 14.378, p < 0.001]. Both effects are abolished in GLAST−/− mice.

To summarize: (1) odor stimulation caused a gamma power decrease in GLAST−/− mice that is almost abolished in GLAST−/− animals. (2) the odor specificity of the oscillatory peaks seen for GLAST+/+ mice during stimulation was lost in GLAST−/− animals.

In contrast to the effects on gamma activity, beta oscillatory activity was low during spontaneous conditions, and only emerged clearly during odor stimulation. We thus extracted significant peaks of beta activity during odor stimulation and compared the values between the two odorants and the two genotypes. During benzaldehyde stimulation, significant peaks were detected in 76% of all trials in GLAST+/+ but only in 64% for GLAST−/− mice. However, hexanal stimulation did not lead to such a difference as significant peaks were detected in 87% of trials for both genotypes.

Normalized power of beta peaks was slightly higher in GLAST+/+ compared to GLAST−/− mice [F(1,173) = 7.864, p < 0.01; Figure 4E]. Mean power was higher for hexanal in GLAST+/+ mice [F(1,101) = 4.964, p < 0.05] but the odorant-related difference was abolished in GLAST−/− mice [F(1,72) = 1.64, p = 0.69]. In addition, peak beta frequencies were slightly higher in GLAST+/+ [21.21 vs. 19.62 Hz; F(1,173) = 5.746, p < 0.05] but not significantly different between the two odorants. Thus in contrast to wild-type mice, beta activity evoked in GLAST−/− mice was lower in intensity, higher in frequency, and did not show specificity to odor.

**EVOKE POTENTIALS BY LOT STIMULATION**

Because oscillations emerge from M/TCs to GCs interactions and were affected by the absence of GLAST, we next examined the state of synaptic transmission at the reciprocal synapses between these cells. Evoked LFPs were recorded in the OB following LOT stimulation. These LFPs have been extensively analyzed in the literature (Rall and Shepherd, 1968; Stripling and Patneau, 1999). Recordings from GC layer showed three phases in the signal: a small brief negative component representing antidromic signal of M/TCs, followed by a large positive component indicative of dendrodendritic excitation of GCs by M/TCs, and finally a late negative wave that represents inhibition on M/TCs.

In this work, we studied the contribution of GLAST to olfactory processing in vivo in adult animals. Since astrocytes express GLAST in both glomerular and EP layers, we functionally evaluated the two layers by recording the spatial distribution of metabolic activity in superficial layers and synchronized electrical activity in deeper layers. We found that in GLAST−/− mice both functions of the OB network are impaired. A schematic summarizing our hypothesis for both metabolic and neuronal impairment in the absence of GLAST is shown in Figure 6.

**DISCUSSION**

In this work, we studied the contribution of GLAST to olfactory processing in vivo in adult animals. Since astrocytes express GLAST in both glomerular and EP layers, we functionally evaluated the two layers by recording the spatial distribution of metabolic activity in superficial layers and synchronized electrical activity in deeper layers. We found that in GLAST−/− mice both functions of the OB network are impaired. A schematic summarizing our hypothesis for both metabolic and neuronal impairment in the absence of GLAST is shown in Figure 6.

**NO APPARENT DEFECT IN OLFACTORY BULB ORGANIZATION IN GLAST−/− MICE**

The regulation of glutamate concentrations is critical during development. Silencing glutamate uptake in GLAST/Glt1 double knockout mice causes multiple brain defects, including cortical, hippocampal and OB disorganization with perinatal mortality (Matsugami et al., 2006). Glt1−/− mice show neuronal damage due to excitotoxicity and undergo premature death because of
Figure 6 | Schematic diagram of the impact of GLAST transporter on olfactory bulb networks. In the GL (upper box), the lack of astrocytic (Ast) glutamate transporter GLAST decreases the uptake of circulating glucose (Glc) during mitral cells (M) activation by glutamate release from the olfactory receptor neurons (ORN). Impairment of glutamate uptake at the level of the granule (GR)-mitral (M) reciprocal synapse (lower box) could lead to an increase of glutamate spillover, provoking the frequency decrease, and power depression of oscillatory activities within the OB circuit in GLAST−/− mice.

Severe epilepsy (Tanaka et al., 1997). However, previous work has shown that GLAST−/− mice do not exhibit such major deficits (Watase et al., 1998) and consistent with this conclusion, our present results show intact OB layers organization and size in this strain. In line with these results, few behavioral deficits have been observed in these animals. GLAST−/− mice are impaired for motor coordination only when they are confronted to the challenging task of a fast rotating rod (Watase et al., 1998). In addition, they are more active in a novel environment and have poor performances in pairwise discrimination learning based on visual cues. In a very simple task of buried food, GLAST−/− mice do not seem to show obvious olfactory defects (Karlsson et al., 2009).

It is noteworthy that GLAST is expressed in the rostral migratory stream by radial glial cells (Hartfuss et al., 2001). These cells guide new cells into the glomerular and GC layers of the OB to renew these interneuronal populations during adult neurogenesis. However in GLAST−/− mice, we found that the volume of both glomerular and GC layers was identical to those in control mice, which would suggest that neurogenesis is not significantly altered when GLAST is absent. In addition, we did not observe upregulation of GLT-1 expression in the OB of GLAST−/− mice, consistently with previous results obtained in the cerebellum (Watase et al., 1998) and the somatosensory barrel cortex (Voutsinos-Porche et al., 2003a). These observations cannot discard the fact that in the GLAST−/− model, newborn neurons could have been affected directly by GLAST deletion at a very fine cellular scale.

Role of GLAST in sensory-evoked metabolic regulation in the olfactory bulb

The identification of precise astrocytic mechanisms involved in supply of glucose to active neuronal networks has received much attention for the past couple of decades (Pellerin and Magistretti, 1994; Bonvento et al., 2002; Figley and Stroman, 2011). The olfactory glomerulus offers a remarkable model to address this issue in the context of sensory-evoked activities, in part because of its unique organization of spherical module with astrocytes positioned at the circumference. We found that the spatial map of olfactory responses to benzaldehyde in the glomeruli identified by radiolabeled 2DG uptake was not different in GLAST−/− mice, which indicates that spatial olfactory coding for this odorant was preserved in these animals. However, the intensity of odor-induced 2DG uptake was reduced in the absence of GLAST. These results are consistent with the decrease in 2DG uptake observed in response to whisker stimulation in the somatosensory cortex of adult rats after local transient downregulation of GLAST using an antisense strategy (Cholet et al., 2001). Since the metabolic response was only partially reduced in GLAST−/− mice, our results do not exclude a possible role of GLT-1 in odor-evoked neurometabolic coupling as was previously reported in the somatosensory cortex (Voutsinos-Porche et al., 2003b) and in the superior colliculus (Hérard et al., 2005). Our results indicate that GLAST participates to the glomerular glucose metabolism in vivo (cf. schematic on Figure 6, upper box).
ROLE OF GLAST IN ODOR-EVOKED OSCILLATIONS IN THE OLFACTORY BULB

Neuronal oscillations are good sensors of the functional state of a network (Singer, 1993; Engel et al., 2001). Two rhythms we focused on (beta: 15–35 Hz and gamma: 60–160 Hz), are classically observed in the OB and have been related to odor processing (Martin et al., 2004; Beshel et al., 2007; Cenier et al., 2008; Aylwin et al., 2009). Cellular basis of gamma activity have been clearly described and rely on the accuracy of GC excitation by M/TC glutamate release, which in turn inhibits M/TC activity via GABA release (Rall and Shepherd, 1968; Neville and Haberly, 2003; Lager et al., 2007).

We find that in mice deleted for the GluTs GLAST, oscillations of the LFP are altered. Gamma bursts, usually prominent in the OB during ongoing activity, exhibits both frequency and power decrease. Odor stimulation leads to a very weak response that has lost its odorant specificity compared to control animals. Together these data suggests a loss of synchrony within the OB circuit, which could be explained by impairment at the level of the reciprocal synapse between M/TCs and GCs. How can the disruption of glutamate uptake into astrocytes specifically impact neuronal network synchrony?

Both experimental and theoretical approaches have demonstrated that synaptic time constants were crucial for the oscillation frequency, and increasing the rise time of inhibition received by M/TCs reduced the frequency of gamma oscillations (Brunel and Wang, 2003; Scanziani et al., 2004; Cenier et al., 2008). One functional consequence of GLAST expression in astrocytes would be the shaping of extracellular glutamate concentration that synaptic receptors are exposed to (Rothstein et al., 1994; Isaacson, 1999), thus the regulation of synaptic spillover mechanism that could impact both pre- and post-synaptic function at the M/TC–GC reciprocal synapse. In the OB, glutamate released from M/TCs can lead to autoreceptor mediated by NMDA and AMPA receptors in addition to the activation of postsynaptic ionotropic receptors (Nicoll and Jahr, 1982; Isaacson, 1999; Salin et al., 2001; Christie and Westbrook, 2006). Thus, regulation of glutamate spillover in the synaptic cleft by GluT may tune the timing of its action on glutamate autoreceptors and may also lead to a change in excitatory input driven by NMDA receptors on GCs (Schoppa et al., 1998) following glutamate release by M/TCs (see Figure 6, lower box, for an illustration). Accordingly, in the hippocampus (Aust et al., 1997; Arnth-Jensen et al., 2002) and cerebellum (Marcaggi et al., 2003), a decrease in glutamate uptake was also shown to affect the activity of NMDA receptors in neighboring synapses.

The recording that we conducted following LOT stimulation strongly supports our expectation that reciprocal synapses have lost their temporal sharpness. Indeed we observed a significantly longer inhibition in GLAST−/− animals suggesting that under electrical stimulation the activation of postsynaptic elements is scattered over time instead of being precisely synchronized. The higher time delay we observed is in accordance with prior observations in the cerebellum, where EPSCs evoked in vitro in Purkinje cells by parallel fiber stimulation are 18% longer in GLAST−/− than in wild-type mice (Marcaggi et al., 2003).

Taken all together, these results suggest that overwhelming glutamate spillover on M/TC–GC synapses could lead to an alteration of the normal neuronal synchrony which is needed to maintain the accuracy of oscillatory activities in the OB.

CHANGES IN CELLULAR AND METABOLIC ACTIVITY IN OLFACTORY BULB NETWORKS OF GLAST−/−

In the OB, astrocytic GluTs were shown to play a key role at the neuromodulatory level (Petzold et al., 2008) regulating odor-evoked blood flow changes and intrinsic optical signals (Gard et al., 2006). Our findings show that knocking out one of these transporters, GLAST, induces an impairment in the odor-evoked glucose uptake as well as in the fine tuning of odor-evoked oscillatory activities in the OB network. In conclusion, we postulate that GLAST participates to the signaling pathways responsible for the dual function of astrocytes in both energy and neuronal information processing in the OB.

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