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Glial membrane channels and receptors in epilepsy: impact for generation and spread of seizure activity

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Abstract

Epilepsy is a condition in the brain characterized by repetitively occurring seizures. While various changes in neuronal properties have been reported to accompany or induce seizure activity in human or experimental epilepsy, other studies suggested that glial cells might be involved in epileptogenesis. Recent findings demonstrate that in the course of the disease, glial cells not only undergo structural alterations but also display distinct functional properties. Several studies identified reduced inwardly rectifying K^+ currents in astrocytes of epileptic tissue, which probably results in disturbances of the K^+ homeostasis. Other data hinted at an abnormal increase in $[Ca^{2+}]_i$ in astrocytes through enhanced activity of glial glutamate receptors. This review summarizes current knowledge of alterations of plasma membrane channels and receptors of macroglial cells in epilepsy and discusses the putative importance of these changes for the generation and spread of seizure activity.

Keywords: Epilepsy; Glial cell; Hippocampus; Ion channel; Glutamate receptor

1. Introduction

Epilepsy comprises a diverse collection of neurological disorders that affects about 1% of the world population. It is a condition in the brain characterized by repetitively occurring seizures, i.e. short-term disturbances of neuronal function associated with motor behavioral abnormalities and disturbances of consciousness. Various changes in neuronal properties have been reported to accompany or induce seizure activity in human or experimental epilepsy. In addition, evidence is accumulating that glial cells might be involved in epileptogenesis (Heinemann et al., 1995; McNamara, 1994), although the mechanisms of the postulated glial contributions are yet poorly understood. Recent advances in functional and molecular techniques considerably improved our understanding of glial physiology. This provides now a basis to identify alterations of glial cell properties in the diseased central nervous system (CNS) and to assess its pathogenic relevance.

Several recent reviews are available that survey the expression of ion channels and receptors by glial cells and debate its potential physiological impact in neuron–glia communication (Carmignoto, 2000; Haydon et al., 2001; Verkhratsky et al., 1998; Verkhratsky and Steinhäuser, 2000). Here we summarize current knowledge of alterations of plasma membrane channels and receptors of macroglial cells in epilepsy, and discuss the putative importance of these changes for the generation and spread of seizure activity.

2. Na^+ channels

Voltage-gated Na^+ channels represent a key prerequisite for the generation of regenerative activity. They are, however, not a privilege of excitable cells but are also present in oligodendrocytes and astrocytes in various CNS regions (reviewed by Verkhratsky and Steinhäuser, 2000). Although the physiological role of glial Na^+ channels is not well understood, it has been proposed that they might serve the regulation of $[Na^+]_i$ and thereby control the activity of Na^+-dependent transporters, e.g. Na^+/glutamate transporters or Na^+/K^+ ATPase (Sontheimer et al., 1994).

Several studies reported changes of Na^+ channel expression in the diseased CNS. A dramatic up-regulation of Na^+ current density was noticed in cultured astrocytes isolated from the seizure focus of human epileptic tissue. The cells possessed depolarised resting membrane potentials and were

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even capable of generating action potential-like responses upon current injection (O'Connor et al., 1998). This let the authors suggest that astrocytes overexpressing Na^+ channels might support the spread of seizure activity through CNS regions in which synaptic transmission was interrupted due to neuronal cell loss. In the acute human epileptic hippocampus, however, the increase in Na^+ current density was less pronounced (Bordey and Sontheimer, 1998). No differences in Na^+ currents were noticed in a comparative patch-clamp analysis of astrocytes in the CA1 region of hippocampus removed from patients either with Ammon's horn sclerosis or lesion-associated epilepsy, two forms of temporal lobe epilepsy (Hinterkeuser et al., 2000). Ammon's horn sclerosis cases were characterized by selective neuronal cell loss and reactive gliosis, while the hippocampus of patients with lesion-associated temporal lobe epilepsy lacked significant histopathological alterations and was used as control-like tissue. Similarly, no increase in astroglial Na^+ current amplitudes was observed in the sclerotic hippocampus of kainate-treated rats, an animal model of temporal lobe epilepsy (Jabs et al., 1997). Thus, the results of the latter two studies did not favour a role for astroglial Na^+ channels in epilepsy. Previous work in cell culture and in situ suggests that astrocytes and neurons, in principle, share a common set of Na^+ channel α-subunits, including $Na_v1.1-1.3$, 1.5 and 1.6 (Black et al., 1994; Black et al., 1998; Oh et al., 1994; Schaller et al., 1995). The molecular identity of glial Na^+ channels in epileptic tissue, however, is still unknown. It remains to be established whether astrocytes associated with epileptic seizure foci express the novel isoform $rNa_v1.5a$ as recently suggested (Gersdorff Korsgaard et al., 2001).

3. Voltage-gated Ca^{2+} channels

Voltage-gated Ca^{2+} channels mediate Ca^{2+} influx upon membrane depolarisation and regulate various intracellular processes in excitable and nonexcitable cells. Based on their functional properties two main groups of Ca^{2+} channels have been distinguished: high-voltage activated (L-, N-, P-, Q- and R-type) and low-voltage activated (T-type) channels. The molecular basis for Ca^{2+} channel diversity arises from different genes encoding the principal, i.e. α1, subunit which forms the voltage-gated transmembrane channel. Based on gene sequence similarity, a nomenclature has been recently suggested that subdivides Ca^{2+} channels into three subfamilies: $Ca_v1.1-1.4$, $Ca_v2.1-2.3$, and $Ca_v3.1-3.3$ (Ertel et al., 2000).

Acutely induced and chronic epilepsies are associated with an enhanced Ca^{2+} influx through neuronal Ca^{2+} channels (Heinemann and Hamon, 1986). During seizure activity, extracellular Ca^{2+} ($[Ca^{2+}]_o$) decreases at the focus site (Heinemann et al., 1977). In acute hippocampal slices, low $[Ca^{2+}]_o$ leads to spontaneous seizure-like neuronal discharge patterns (Haas and Jefferys, 1984; Konnerth et al., 1986) implicating a role for Ca^{2+} in the generation of epileptic activity in vivo. Although the decrease in $[Ca^{2+}]_o$ was usually attributed to Ca^{2+} influx into neurons, different types of Ca^{2+} channels have also been identified in glial cells both in cell culture and in various acute preparations (Verkhratsky et al., 1998; Verkhratsky and Steinhäuser, 2000). Ca^{2+} channels in neurons are inhibited by anticonvulsant drugs (Elliott, 1990; Schumacher et al., 1998; Yaari et al., 1986). Similarly, in cultured astrocytes, depolarisation-induced increases in intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) were reduced upon co-application of anticonvulsant compounds such as phenytoin, valproate or flunarizine at therapeutically relevant concentrations (White et al., 1992). The latter authors speculated that in addition to neurons, Ca^{2+} channels in astrocytes might contribute to $[Ca^{2+}]_o$ depletion during seizure activity and represent a target of antiepileptic drugs. In favour of this hypothesis, immunostaining noted an upregulation of astrocytic L-type Ca^{2+} channels in the kainate model of epilepsy, suggesting enhanced uptake of extracellular Ca^{2+} by astrocytes in the lesioned CNS in vivo (Westenbroek et al., 1998). This suggestion appears reasonable since electrophysiology and microfluorometry basically confirmed the presence of different types of functional Ca^{2+} channels in oligodendrocytes and astrocytes after fresh isolation or in situ (Akopian et al., 1996; Berger et al., 1992; Duffy and MacVicar, 1994; Newman, 1985). In addition to the presumed rapid and direct contribution to seizure generation via depletion of $[Ca^{2+}]_o$, Ca^{2+} influx through Ca^{2+} channels in astrocytes is likely to add to the synthesis and release of transmitters, cytokines and growth factors, thereby indirectly influencing the architecture and activity of neural circuitry on a long term.

4. K^+ channels

Among the ion channel families, the K^+ channel superfamily is by far the largest and most diverse one. It consists of three groups of K^+ channel α subunits: those having six transmembrane domains (including the subfamilies of Ca^{2+}-activated and voltage-activated K^+ channels), those with four transmembrane domains (two pore tandem channels) and those with two transmembrane domains (inwardly rectifying K^+ channels (K_{IR} channels); for review see Coetzee et al., 1999). Most of these α subunits are able to form heteromeric complexes, which results in a tremendous variety of K^+ channels with different functional properties.

During neuronal activity, $[K^+]_o$ is temporarily enhanced, causing depolarization of nearby membranes, which, if uncorrected, would produce neuronal hyperactivity. The clearance of K^+ from the extracellular space is considered an important function of glial cells (Walz, 1989; Walz, 2000) and a long standing hypothesis proposes that gliosis produces or adds to seizure activity (Pollen and Trachtenberg, 1970). Seizure activity in vivo is characterized by significant elevations of $[K^+]_o$ (up to about 10 mM; Fisher

et al., 1976; Lothman and Somjen, 1976; Moody et al., 1974) and high levels of $[K^+]_o$ are sufficient to trigger seizure-like events in the hippocampal CA1 field (Traynelis and Dingledine, 1988). Buffering of $[K^+]_o$ has been analysed in different model systems (Gardner-Medwin et al., 1981; Kettenmann et al., 1987; Kuffler et al., 1966), and Newman (1986, 1993) identified K_{IR} channels as an important prerequisite for this glial function.

Because of its presumed impact on neuronal excitability, various studies have investigated properties of astroglial K_{IR} channels in the normal (Bordey and Sontheimer, 1997; Bringmann et al., 1999; Gabriel et al., 1998b; Kressin et al., 1995) and diseased CNS (Bordey et al., 2001; D'Ambrosio et al., 1999; Francke et al., 1997; Schröder et al., 1999). This work revealed a considerable up-regulation of inwardly rectifying K^+ conductances ($g_{K(IR)}$) in astrocytes during postnatal development while brain damage and disease consistently led to a reduction of inward rectification in these cells (Fig. 1A,B).

The regulation of inwardly rectifying K^+ currents ($I_{K(IR)}$) has also been investigated in experimental and human epilepsy. In the kainate-lesioned hippocampus, no or only minor changes in astroglial $I_{K(IR)}$ have been reported (Jabs et al., 1997; see also Burnard et al., 1990) and another study suggested that in this condition, passive KCl fluxes and Na^+/K^+ ATPase contributed to astroglial K^+ uptake (Walz and Wuttke, 1999). However, in the pilocarpine model, effects of Ba^{2+} on stimulus induced changes in $[K^+]_o$ suggested a significant reduction of $I_{K(IR)}$ in astrocytes of the CA1 area of epileptic rats (Gabriel et al., 1998a). These findings were in line with experiments investigating hippocampal tissue obtained from patients with pharmaco-resist-

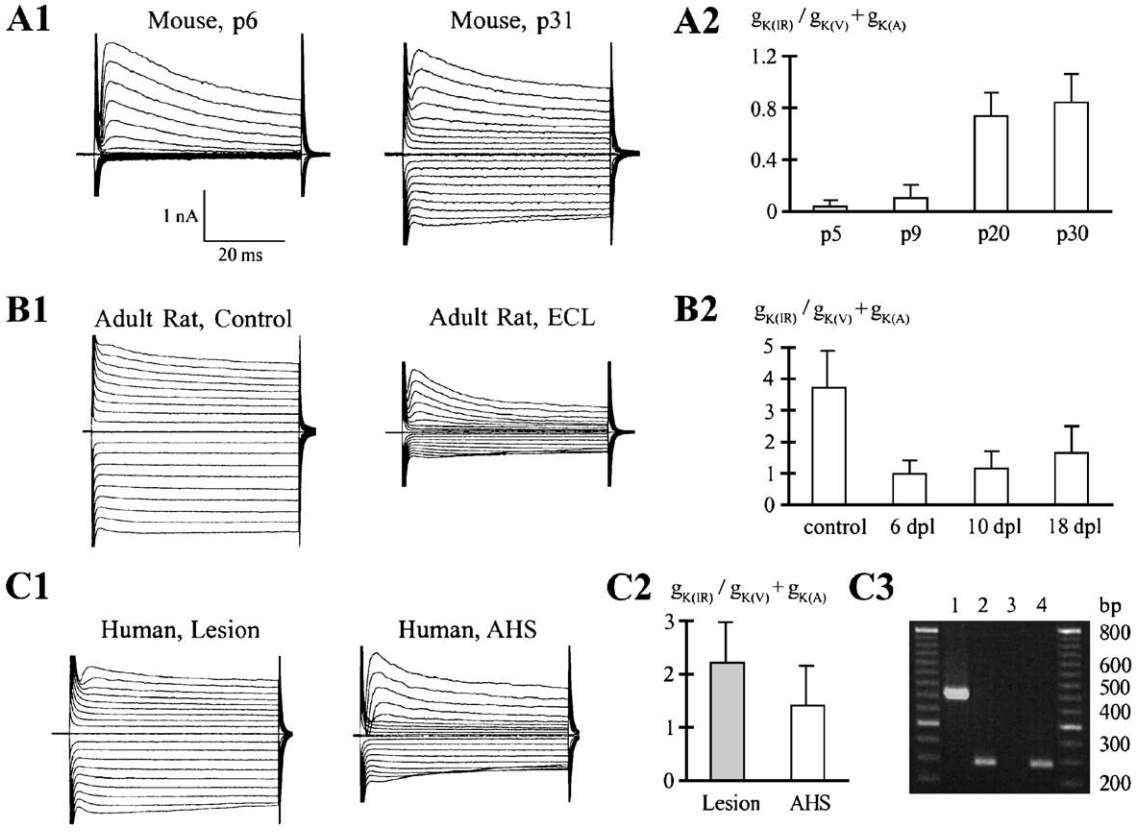

Fig. 1. Regulation of astroglial $I_{K(IR)}$ during ontogenesis, after lesion, and in human temporal lobe epilepsy. (A1) Comparative recordings from hippocampal astrocytes at different postnatal ages. Currents were activated by stepping the membrane between −160 and +20 mV, revealing an increase in $I_{K(IR)}$ amplitudes during development. (A2) After subtraction of background currents, $g_{K(IR)}$ and outward K^+ conductance ($g_{K(V)}+g_{K(A)}$) were calculated at −130 and +20 mV. Comparing the ratio of $g_{K(IR)}/(g_{K(V)}+g_{K(A)})$ during development revealed a significant increase in the relative contribution of $g_{K(IR)}$ beyond p9. For details see Kressin et al. (1995). (B1) Current pattern of astrocytes in the dentate gyrus of adult control rats and after entorhinal cortex lesion (ECL). Currents were evoked as described in (A1). Prominent background currents and $I_{K(IR)}$ were activated in the control astrocyte while reduced inward rectification was evident after ECL. (B2) $g_{K(IR)}$ and $g_{K(V)}+g_{K(A)}$ were determined as described in (A2). Between 6 and 18 days post lesion (dpl), the ratio $g_{K(IR)}/(g_{K(V)}+g_{K(A)})$ was significantly lower than in control astrocytes. For details see Schröder et al. (1999). (C1) Current pattern of hippocampal astrocytes obtained from patients with lesion-associated epilepsy and Ammon's horn sclerosis (AHS; same protocol as described in (A1)). (C2) $g_{K(IR)}$ and $g_{K(V)}+g_{K(A)}$ were calculated as described in (A2). A significantly reduced ratio $g_{K(IR)}/(g_{K(V)}+g_{K(A)})$ was observed in Ammon's horn sclerosis. (C3) Subsequent to the recording the cytoplasm of human cells was harvested and probed for Kir4.1 and β-actin transcripts. An astrocyte contained mRNAs encoding Kir4.1 (lane 1) and β-actin (lane 2). In contrast, transcripts for the housekeeping gene, β-actin (lane 4), but not for Kir4.1 (lane 3) were detected in a neuron. For details see Schröder et al. (2000).

ant temporal lobe epilepsy. Using the same experimental approach, this group noted an impaired regulation of $[K^+]_o$ in the highly sclerotic CA1 region of patients with Ammon's horn sclerosis as compared to either the less morphologically altered dentate gyrus of the same patients (Gabriel et al., 1998c) or the CA1 area of non-Ammon's horn sclerosis patients showing only minor histopathological changes (Kivi et al., 2000). The authors' hypothesis that diminished astroglial $g_{K(IR)}$, rather than alterations in passive KCl uptake or Na^+/K^+ ATPase activity, underlies the reduced $[K^+]_o$ buffering in sclerosis (Jauch et al., 2002) was confirmed by patch-clamp studies that allowed to quantify intrinsic membrane properties in the two forms of epilepsy (Bordey and Sontheimer, 1998; Hinterkeuser et al., 2000). Subsequent transcript analysis identified the subunit Kir4.1 in human astrocytes (Schröder et al., 2000) (Fig. 1C). However, a co-expression of other subunits in human astrocytes is very likely. Indeed, recent data suggested a functional expression of astroglial Kir6/SUR channels in human hippocampus (Steinhäuser et al., 2000) and the subunits Kir2.1–2.3 have been found in mouse astrocytes (Schröder et al., 2002). The question which of the multiple Kir subunits are affected in sclerosis to produce reduced inward rectification still has to be answered although preliminary data identified Kir4.1 as a potential candidate (Seifert et al., 2002b). It remains as yet unclear whether increased astroglial proliferation or rather dedifferentiation of formerly mature cells constitutes the basis for the observed loss of astroglial inward rectification in epileptic tissue. However, it has to be noted that reduced $g_{K(IR)}$ was found to accompany mitotic activity of astrocytes in lesion models both in vitro (MacFarlane and Sontheimer, 1997) and in situ (Bordey et al., 2001). In conclusion, evidence showing reduced astroglial $I_{K(IR)}$ in sclerotic epileptic tissue is accumulating. This alteration in conjunction with a seizure-induced shrinkage of the extracellular space (Lux et al., 1986) leads to an impaired spatial K^+ buffering, resulting in stronger and prolonged depolarisation of glial cells and neurons in response to activity-dependent K^+ release. Thus, modified properties of astrocytes might directly contribute to or even initiate seizure generation and seizure spread in hippocampal sclerosis (McNamara, 1994).

While most studies agreed in reporting a significant down-regulation of astroglial $I_{K(IR)}$ in epileptic tissue, findings on outward K^+ currents are less consistent. A decreased delayed rectifier K^+ conductance ($g_{K(V)}$) was found in astrocytes of the kainate-lesioned hippocampus (Jabs et al., 1997). In human epilepsy, enhanced transient K^+ current ($I_{K(A)}$) densities and decreased delayed rectifier K^+ current ($I_{K(V)}$) densities have been reported in glial cells (Bordey and Sontheimer, 1998). While the latter study was based on a relatively small sample size and pooled cells from different cortical areas, another group failed to find corresponding changes when comparing properties of human astrocytes in a more restricted brain region, the stratum radiatum of the hippocampal CA1 region (Hinterkeuser et al., 2000). These authors noted, however, a negative shift of steady-state activation and inactivation of $I_{K(A)}$ in Ammon's horn sclerosis as compared to patients with lesion-associated temporal lobe epilepsy.

5. Gap junction channels

Gap junctions are intercellular transmembrane channels that allow electrical and chemical communication between coupled cells. Among the large number of different connexin genes found in the nervous system so far (Rozental et al., 2000), only some are thought to be expressed in a cell-type-specific manner. Cx43 represents the principal gap junction protein in astrocytes (Giaume and McCarthy, 1996) and Cx30 was found to be co-expressed in this cell type at late stages of development (Kunzelmann et al., 1999; Nagy et al., 1999). Oligodendrocytes express Cx32 which, however, may also occur in neurons (Dermietzel et al., 1989). The idea that electrotonic coupling between neurons might have a role in the generation and maintenance of seizure activity has recently gained new relevance (Velazquez and Carlen, 2000).

Gap junction coupling among astrocytes appears to be essential for proper regulation of the K^+ homeostasis in the CNS (Orkand, 1986). Moreover, gap junctions in astrocytes are involved in the spread of intracellular Ca^{2+} waves through glial networks and thereby may influence neuronal activity (Carmignoto, 2000; Haydon et al., 2001). Glial Ca^{2+} waves, the physiological relevance of which recently has been confirmed in acute brain slices (Newman and Zahs, 1997; Schipke et al., 2002), may also travel into regions that are not synaptically connected. These findings, however, also suggested that increased astroglial coupling might support hypersynchronization and spread of neuronal discharges during seizure activity. Several studies investigated a putative role of astroglial gap junctions in epilepsy. Using the Fluorescence Recovery After Photobleach (FRAP) method, Lee et al. (1995) observed increased gap junction coupling between cultured astrocytes that were originally obtained from human epileptic specimens and the authors attributed this increase in coupling efficacy to an enhanced expression of Cx43 protein in epileptic astrocytes. However, findings on connexin expression in glial cells of human epileptic tissue remained inconsistent. Northern analysis of tissue resected from patients suffering from intractable temporal lobe epilepsy found a threefold enhanced level of Cx43 mRNA (Naus et al., 1991) but in other studies, neither the Cx43 transcript nor the protein content was upregulated in epileptic temporal lobe specimens (Elisevich et al., 1997b). Hence, the latter authors concluded that the clinical outcome was independent of astroglial Cx43 content. This conclusion was in line with the data obtained from different animal models of temporal lobe epilepsy since no long-lasting changes in the expression of Cx43, Cx32 or Cx30 were found in kindled, kainate-treated and tetanus

toxin-treated rats (Elisevich et al., 1997a; Khurgel and Ivy, 1996; Söhl et al., 2000). A short-term decrease of Cx43 transcripts, however, was observed in the kainate model of temporal lobe epilepsy (Khurgel and Ivy, 1996).

Besides alterations in the expression level, coupling efficacy depends on the permeability of gap junction channels which is modulated by various intracellular parameters such as the pH or second messengers (Velazquez and Carlen, 2000). Interestingly, intracellular acidification was observed to terminate epileptiform activity (Xiong et al., 2000). It is thus conceivable that subtle, local changes in gap junction function determine the effective level of hyperactivity in seizure-prone tissue while the overall connexin expression level remains unchanged.

6. Glutamate receptors

Glutamate is the principal excitatory transmitter in the mammalian brain and activates metabotropic and ionotropic receptors. Various studies have suggested the possible involvement of glutamate receptors in seizure development and spread, and increased extracellular levels of glutamate have been found in epileptogenic foci (Glass and Dragunow, 1995). Hence, these receptors have been considered promising targets in approaches aimed at controlling hyperexcitability. While earlier studies usually focussed on neurons, recent work has proven that functional metabotropic and ionotropic glutamate receptors are also expressed by glial cells (Steinhäuser and Gallo, 1996) and knowledge about their putative involvement in epilepsy is now gradually emerging.

6.1. Metabotropic glutamate receptors

The metabotropic glutamate receptor family consists of eight members, $mglu_1$ to $mglu_8$, which couple to GTP-binding proteins and can be classified into three groups based on sequence homology. Group I comprises $mglu_1$ and $mglu_5$ and their activation leads to stimulation of phospholipase C, increase in intracellular IP_3 level and release of Ca^{2+} from internal stores. Group II ($mglu_2$, $mglu_3$) and group III ($mglu_{4,\ 6,\ 7,\ 8}$) receptors are negatively coupled to adenylate cyclase (reviewed by Pin and Duvoisin, 1995). $mglu_3$ and $mglu_5$ are the predominant subtypes of metabotropic glutamate receptors in glial cells (Schools and Kimelberg, 1999; Winder and Conn, 1996).

In animal models of temporal lobe epilepsy, reactive astrocytes of the hippocampus were characterized by a persistent upregulation of $mglu_3$ and $mglu_5$ proteins (Aronica et al., 2000; Ferraguti et al., 2001; Ulas et al., 2000), probably mediated by cytokines and trophic factors that are elevated in epileptic tissue (Gall et al., 1997; Miller et al., 1995). In addition, the group III receptor, $mglu_8$, was induced in astrocytes after pilocarpine-induced epilepsy (Tang et al., 2001). $mglu_3$ and $mglu_5$ proteins were also found in astrocytes of 'normal' human hippocampus (Blümcke et al., 1996) and electron microscopy identified $mglu_{2/3}$, $mglu_4$ and $mglu_8$ in hippocampal astrocytes of patients with temporal lobe epilepsy, suggesting an involvement of these receptors in gliosis (Tang and Lee, 2001). Indeed, activation of $mglu_5$ and $mglu_3$ has been found to stimulate or decrease proliferation of cultured astrocytes (Ciccarelli et al., 1997).

Frequent activation of $mglu_5$ during seizures enhanced IP_3 hydrolysis in astrocytes and increased $[Ca^{2+}]_i$ (Ong et al., 1999). Group I metabotropic glutamate receptors are critically involved in the induction of glial Ca^{2+} oscillations (Bezzi et al., 1998; Pasti et al., 1997) and receptor activation induced astroglial swelling (Hansson, 1994). Moreover, glial Ca^{2+} waves may travel over long distances, induce glial glutamate release and influence neuronal excitability (see above). Thus, upregulation of group I metabotropic glutamate receptors in astrocytes as observed in epilepsy suggests its involvement in seizure generation or spread, although direct evidence for this hypothesis is still outstanding.

On the other hand, enhanced activation of $mglu_3$ in astrocytes might have neuroprotective effects, presumably mediated by release of transforming growth factor (TGF-β; Bruno et al., 1998). This mechanism might also be operative in epilepsy since in a rat model of temporal lobe epilepsy, upregulation of $mglu_3$ was accompanied by enhanced expression of TGF-β (Aronica et al., 2000). This growth factor also promotes neurite sprouting (Ishihara et al., 1994) and it is tempting to speculate that increased release of TGF-β upon enhanced $mglu_3$ activation might contribute to the reorganisation of neuronal circuitry typically observed in the epileptic brain.

6.2. Ionotropic glutamate receptors

Based on their pharmacological and biophysical properties, ionotropic glutamate receptors have been subdivided into three families: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate and *N*-methyl-D-aspartate (NMDA) receptors. The gating of glutamate receptors leads to depolarization via activation of a nonselective cationic conductance. The receptors are composed of four subunits (Rosenmund et al., 1998) that within one family form homomeric or heteromeric receptors. AMPA receptors are encoded by four different genes (GluR1–GluR4), kainate-preferring receptors by five genes (GluR5–GluR7, KA1 and KA2) and NMDA receptors by at least six genes (NR1, NR2A–NR2D, NR3).

Glial cells express functional ionotropic glutamate receptors of the AMPA subtype (Seifert and Steinhäuser, 2001; Verkhratsky and Steinhäuser, 2000) which are activated by synaptically released glutamate (Bergles et al., 2000; Porter and McCarthy, 1996). Astrocytic AMPA receptors are Ca^{2+}-permeable (Backus and Berger, 1995; Jabs et al., 1994; Seifert and Steinhäuser, 1995). In culture, ionotropic

glutamate receptor activation induced a rise in $[Ca^{2+}]_i$ and triggered Ca^{2+} oscillations that propagated through the glial network (Cornell-Bell et al., 1990; Dani et al., 1992). AMPA receptors in astrocytes in situ contribute to the stimulation of glial glutamate release, a process that is Ca^{2+}-dependent (Bezzi et al., 1998).

Functional properties of AMPA receptors were analysed in astrocytes of the hippocampus resected from patients with Ammon's horn sclerosis and comparative recordings were performed in cells from patients with lesion-associated temporal lobe epilepsy. Reversal potential analysis of the receptor currents revealed no difference in Ca^{2+} permeability of the glial receptors in the two forms of temporal lobe epilepsy with the divalent to monovalent permeability ratio, P_{Ca}/P_{Cs}, amounting to about 0.3 (Seifert et al., 2002a). This value was comparable to data obtained from rodent hippocampus (Seifert and Steinhäuser, 1995) and suggested an invariable expression of the Ca^{2+} impermeable GluR2 subunit, irrespective of the form of epilepsy.

A diversity in receptor functioning results from posttranscriptional alterations of GluR genes, such as pre-mRNA editing and alternative splicing. Editing of the Q/R site of GluR2 confers a low Ca^{2+} permeability to channel complexes containing this subunit (Burnashev et al., 1992). Mouse mutants with deficient Q/R editing developed early-onset epilepsy with spontaneous and recurrent seizure activity (Brusa et al., 1995), suggesting that enhanced Ca^{2+} influx through AMPA receptors reduces seizure threshold. However, the above data (Seifert et al., 2002a) and findings of another group (Kortenbruck et al., 2001) are not in favour of the idea that GluR2 editing in astrocytes plays a role in human epilepsy although unedited GluR2 transcripts have been identified in the hippocampus of young Ammon's horn sclerosis patients (Grigorenko et al., 1998). The four AMPA receptor subunits each occur as two different splice versions, flip and flop, that possess different gating characteristics (Mosbacher et al., 1994). Receptors carrying the flip form show a slower desensitisation kinetics than those composed of flop and are more sensitive to the specific AMPA receptor modulator cyclothiazide. Taking advantage of this compound, an enhanced portion of flip versions of AMPA receptor has been identified in hippocampal astrocytes of Ammon's horn sclerosis specimens as compared to patients with lesion-associated temporal lobe epilepsy (Fig. 2). The proportion of flip increases during postnatal astroglial maturation (Seifert et al., 1997) and is thus further up-regulated in sclerosis. Hence, astrocytes of Ammon's horn sclerosis patients possess prolonged AMPA receptor

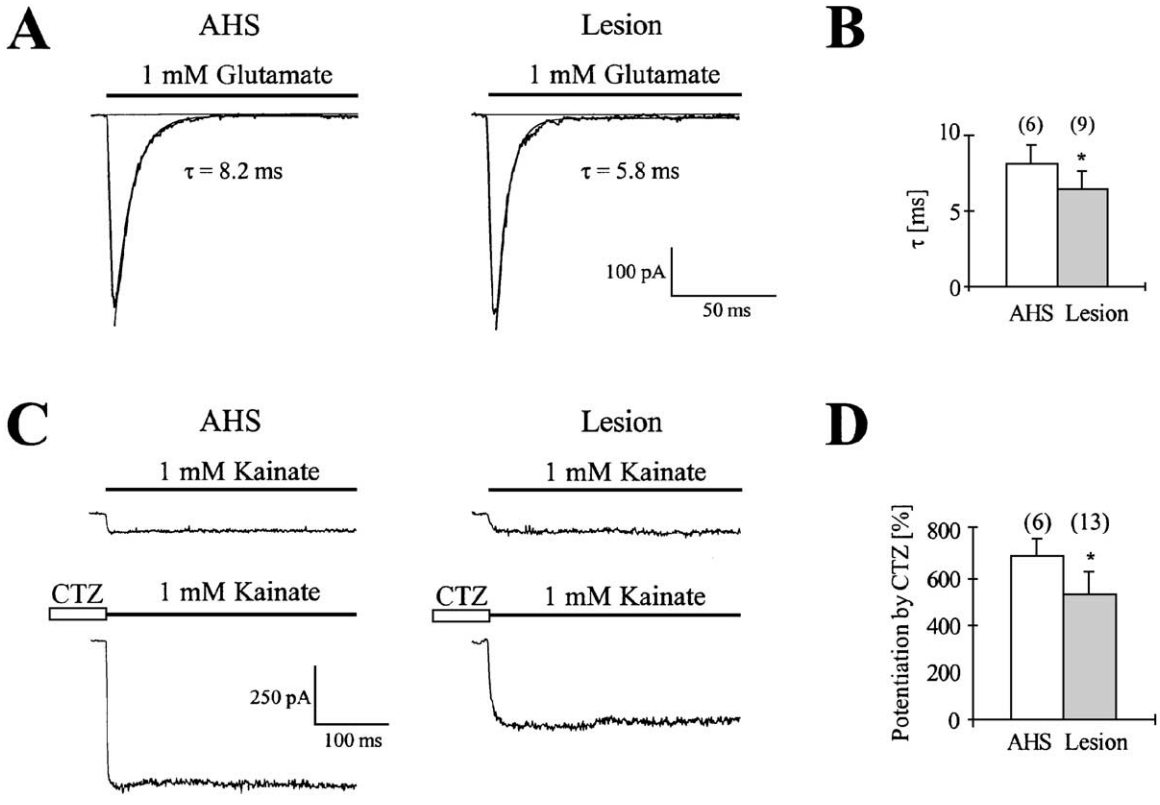

Fig. 2. Case-dependent expression of flip/flop AMPA receptor splice variants in astrocytes from epilepsy patients. (A, B) Fast application of glutamate evoked inward currents in CA1 hippocampal astrocytes from patients with Ammon's horn sclerosis (AHS) and lesion-associated epilepsy ($V = -70$ mV). Current desensitisation was significantly (*) faster in the lesion group as compared with Ammon's horn sclerosis. (C) After kainate application, the cells were exposed to cyclothiazide (CTZ, 100 μM) for 30 s and then kainate was applied again. In the Ammon's horn sclerosis cell, cyclothiazide potentiation amounted to 790% whereas a much lower amplification was observed in the lesion cell. (D) The difference in potentiation between Ammon's horn sclerosis and lesion-associated epilepsy was statistically significant (*). Cell numbers are given in parentheses. From: Seifert and Steinhäuser (2001), with permission.

responses, predicting enhanced depolarisation upon activation by endogenously released glutamate. These changes might contribute to the increased Ca^{2+} oscillations and Ca^{2+} wave propagation observed in human glial cells cultured from epileptogenic foci (Gunel et al., 1991). Enhanced influx of Ca^{2+} through astroglial AMPA receptors can thus be expected to add to seizure generation in this particular condition of human temporal lobe epilepsy. It has also to be considered that prolonged receptor opening will promote influx of Na^+ ions and plug astroglial K_{IR} channels (Schröder et al., 2002), which will further strengthen depolarisation and reduce the K^+ buffer capacity of astrocytes.

Astrocytes cultured from patients with Rasmussen's encephalitis, a rare form of childhood epilepsy, also showed spontaneous Ca^{2+} oscillations that were dependent on transmembrane influx of Ca^{2+} (Manning and Sontheimer, 1997). The authors speculated that these responses, possibly due to autocrine ionotropic glutamate receptor stimulation by glutamate released from astrocytes, might add to neuronal hyperactivity. Another study suggested that the destruction of astrocytes by GluR3 antibodies plays a critical role in

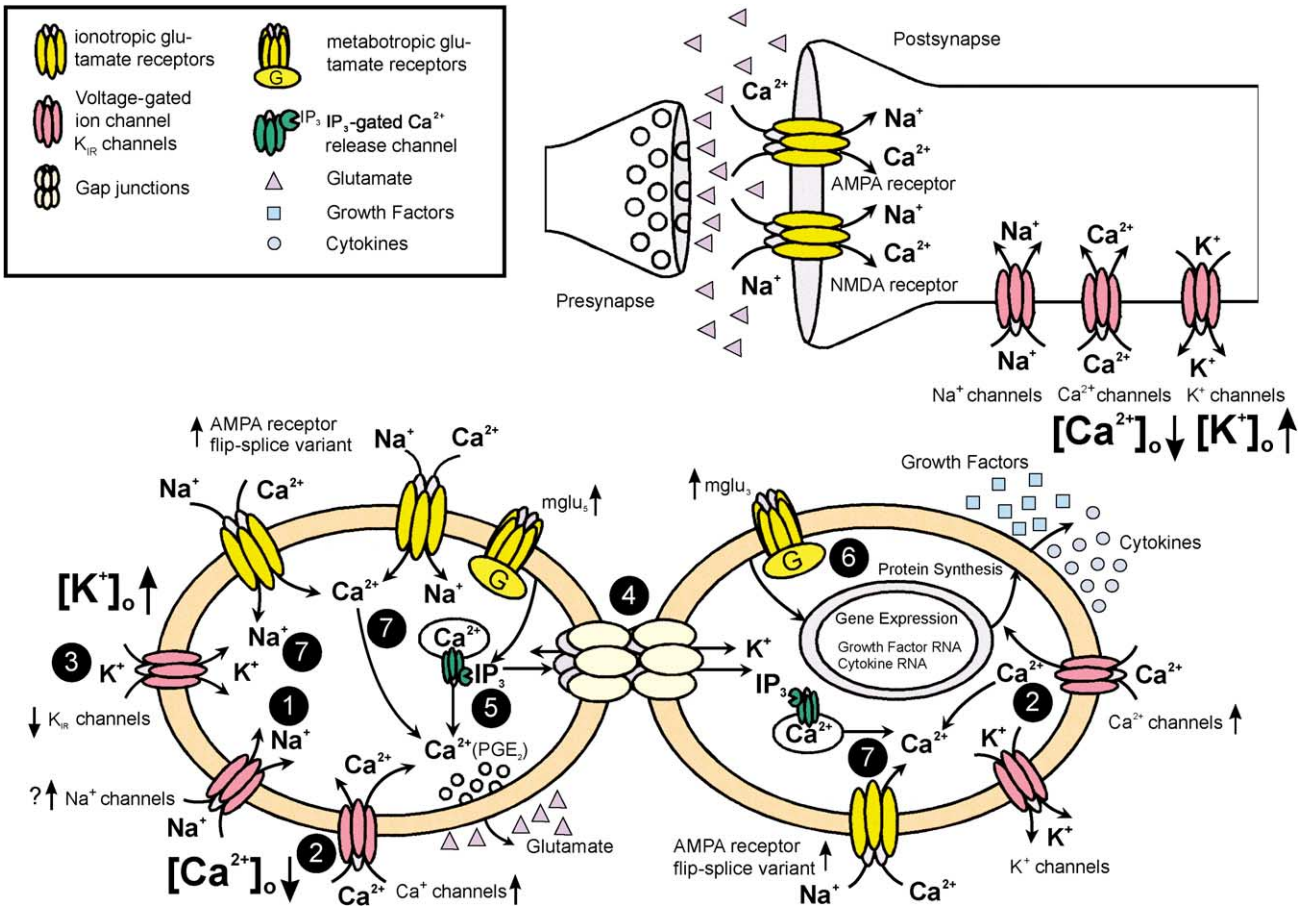

Fig. 3. Epilepsy-associated alterations of functional properties in glial cells. Neuronal hyperactivity produces enhanced release and spillover of glutamate, increase in $[K^+]_o$ and a reduction of $[Ca^{2+}]_o$. (1) Upregulation of Na^+ channels in astrocytes of the sclerotic hippocampus might enhance $[Na^+]_i$ and modulate the activity of Na^+-dependent transporters in the glial membrane. (2) During seizure activity, $[Ca^{2+}]_o$ decreases at the focus site. Astroglial Ca^{2+} channels are upregulated in experimental epilepsy, suggesting that part of the extracellular Ca^{2+} depletion is due to enhanced influx of Ca^{2+} into glial cells through Ca^{2+} channels. Enhanced $[Ca^{2+}]_i$ might promote the production and release of transmitters, cytokines and growth factors from astrocytes. (3) Epileptiform activity is accompanied by an increase in $[K^+]_o$. Downregulation of K_{IR} channels was observed in astrocytes at the seizure site, leading to an impaired clearance of K^+ ions from the extracellular space and to stronger neuronal depolarization. (4) Glial gap junction coupling is involved in the propagation of intracellular Ca^{2+} waves, transmitter release and neuronal activation, and thus might contribute to seizure spread. Clear evidence for an upregulation of gap junctions in epileptic tissue is still missing. (5) Astroglial $mglu_5$ is upregulated in animal models of epilepsy, which enhanced IP_3 hydrolysis, induced Ca^{2+} oscillations and led to glutamate release through a prostaglandin E_2 (PGE_2)-dependent mechanism. This might strengthen the cascade described in (4). (6) Enhanced expression of $mglu_3$ was observed in astrocytes of epileptic tissue, suggesting the induction of gene expression and protein synthesis of growth factors and cytokines. Release of these factors from glial cells probably contributes to the reorganisation of the neuronal circuitry. (7) Astrocytes in human Ammon's horn sclerosis primarily express the flip forms of AMPA receptors, leading to an enhanced influx of Ca^{2+} and Na^+. Coactivation of AMPA receptors and metabotropic glutamate receptors linked to the IP_3–Ca^{2+} cascade stimulates Ca^{2+}-dependent glutamate release and generates Ca^{2+} waves in glial cells. The AMPA receptor-mediated increase in $[Na^+]_i$ mediates an inhibition of K_{IR} channels and reduces the K^+ buffer capacity of astrocytes.

the progression of this autoimmune disorder (Whitney and McNamara, 2000).

7. Conclusions

Glial cells in the brain undergo distinct morphological alterations in epilepsy. Evidence is now accumulating that the structural changes are accompanied by variations in glial functioning (cf. Fig. 3). These cells express a set of ion channels and receptors similar to their neuronal counterpart, and alterations of gating properties or expression levels of these channels might be involved in the pathogenesis of the disease. In this context, the increasing evidence of impaired K^+ buffering due to reduced $g_{K(IR)}$ in astrocytes of sclerotic epileptic hippocampus deserves particular attention. In fact, surgical removal of sclerotic tissue often results in a significant improvement of the epileptic condition, suggesting that gliosis contributes to seizure generation. It remains an important issue to figure out what factor(s) initiate the down-regulation of glial $I_{K(IR)}$ and whether this change is causative for the development of the disease. The impact of other glial alterations on the epileptic condition is less clear. As an example, enhanced expression of the astroglial gap junction protein Cx43 might improve spatial K^+ buffering, thereby counteracting seizure development. On the other hand, increased coupling was assumed to support hypersynchronization and exacerbate seizure activity. Both neuroprotective and pro-convulsive effects have also been reported to result from enhanced activation of astrocytic metabotropic glutamate receptors in epilepsy, with changes in $[Ca^{2+}]_i$ being of particular importance. In conclusion, astrocytes and oligodendrocytes are highly plastic cell types that undergo various, parallel functional changes in the course of a disease (Fig. 3). Promising approaches in analysing the role of glial cells in epilepsy have to consider these multiple mechanisms as well as subregional peculiarities defined by the cell's specific microenvironment.

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