Epilepsy in patients with a brain tumour: focal epilepsy requires focused treatment

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Brain tumours frequently cause epileptic seizures. Medical antiepileptic treatment is often met with limited success. Pharmacoresistance, drug interactions and adverse events are common problems during treatment with antiepileptic drugs. The unpredictability of epileptic seizures and the treatment-related problems deeply affect the quality of life of patients with a brain tumour. In this review, we focus on both clinical and basic aspects of possible mechanisms in epileptogenesis in patients with a brain tumour. We provide an overview of the factors that are involved in epileptogenesis, starting focally at the tumour and the peritumoral tissue and eventually extending to alterations in functional connectivity throughout the brain. We correlate this knowledge to the known mechanisms of antiepileptic drugs. We conclude that the underlying mechanisms of epileptogenesis in patients with a brain tumour are poorly understood. The currently available antiepileptic drugs have little to no influence on the known epileptogenic mechanisms that could contribute to the poor efficacy. Better understanding of focal changes that are involved in epileptogenesis may provide new tools for optimal treatment of both the seizures and the underlying tumour. In our opinion, therapy for every patient with a brain tumour suffering from epilepsy should first and foremost aim at eliminating the tumour as well as the epileptic focus through resection combined with postoperative treatment, and only if this strategy does not result in adequate seizure control should medical antiepileptic treatment be intensified. If this strategy, however, results in sustained seizure freedom, tapering of antiepileptic drugs should be considered in the long term.

Keywords: epilepsy; brain tumour; antiepileptic drugs; epileptogenesis
Abbreviation: GABA = γ-aminobutyric acid

Introduction

Brain tumours may arise from brain tissue (primary brain tumours, e.g. astrocytic, oligodendroglial and glioneuronal tumours) or from malignancies elsewhere in the body, e.g. lung cancer and melanoma (secondary brain tumours). Seizures are a frequent symptom in patients with a brain tumour. The incidence varies between 30% and 100% and depends on the tumour type, with slow-growing tumours being the most epileptogenic (van Breemen et al., 2007). The impact of epilepsy on the total disease burden is high and additionally, both epilepsy and the use of antiepileptic drugs predispose to deterioration of cognitive function (Klein et al., 2003), already a major problem in patients with a brain tumour (Douw et al., 2009; Hilverda et al., 2010).
The specific events that occur in a lesion and lead to seizures are unknown. Many studies have assessed the efficacy of antiepileptic drugs, but relatively few have investigated the mechanisms that underlie epileptogenesis. Altogether, little progress has been made in recent years and many patients with a brain tumour with epilepsy suffer from ongoing seizures due to pharmacoresistance. In a large cohort study, complete seizure control was achieved in only 20 of 158 (12.6%) patients with a brain tumour (Hildebrand et al., 2005). In 15–58% of cases of low-grade glioma, the epilepsy appears to be intractable (Duffau et al., 2002).

Understanding the mechanisms that underlie epileptogenesis in brain tumours is essential to identify new treatment targets and to develop effective treatment. In this review we will comment on the current state regarding the treatment of both epilepsy and tumour, and review the current knowledge on underlying mechanisms of epileptogenesis in patients with a brain tumour. Further, we provide suggestions for optimal treatment and future research.

Current state: treatment of epilepsy

Efficacy of antiepileptic drugs in patients with a brain tumour

Currently, the management of epilepsy in patients with a brain tumour mainly relies on antiepileptic drug therapy. Antiepileptic drugs can be divided into two groups: first generation drugs (e.g. phenytoin, carbamazepine, valproic acid, ethosuximide, benzodiazepines and barbiturates) and second generation drugs (e.g. levetiracetam, felbamate, gabapentin, lamotrigine, pregabalin, tiagabin, zonisamide, oxcarbazepine and topiramate). The vast majority of antiepileptic drugs are thought to modulate inhibitory neurotransmission, in most cases voltage-gated ion channels. These channels include sodium, calcium and potassium channels (Table 1). Some antiepileptic drugs enable  \( \gamma \)-aminobutyric acid (GABA)ergic neurotransmission (e.g. benzodiazepines, barbiturates, felbamate and topiramate) and thereby enhance neuronal inhibition. Other antiepileptic drugs enhance neuronal inhibition by decreasing GABA metabolism (valproic acid), preventing GABA reuptake (tiagabin) or increasing GABA synthesis (valproic acid, gabapentin) (Meldrum and Rogawski, 2007; White et al., 2007). Only two antiepileptic drugs (felbamate and topiramate) modulate the excitatory neurotransmission by modulating glutamate receptors such as AMPA [(2-amino-3-((5-methyl-3-oxo-1,2-oxazol-4-yl)propanoic acid)], N-methyl-D-aspartate and kainate receptors.

The efficacy of antiepileptic drugs has been investigated in the general epilepsy population and there are extensive guidelines on treatment in this population. Unfortunately, large randomized studies of the efficacy of antiepileptic drugs in patients with a brain tumour are scarce, although with the development of newer antiepileptic drugs, more studies on the efficacy of these drugs have been carried out. The majority of research has focused on levetiracetam, both as add-on therapy as well as monotherapy (Patsalos, 2000). In an early report, Wagner et al. (2003), prospectively followed 26 patients with a brain tumour and found that a seizure reduction of >50% was achieved with levetiracetam in 65% of the patients, whereas seizure freedom was seen in 20%. In other studies with levetiracetam, e.g. by Maschio et al. (2006) and Newton et al. (2006) in 19 and 41 patients with a brain tumour, respectively, a reduction in seizure frequency of >50% was found in 72% and 90%, respectively. More recent studies showed similar percentages (Dinapoli et al., 2009; Maschio et al., 2010a; Rosati et al., 2010; Usery et al., 2010). Other drugs investigated in patients with a brain tumour are topiramate, pregabalin, gabapentin,

| Table 1 Proposed mechanisms of action of anti-epileptic drugs and associated epilepsy syndromes |
|-----------------------------------------------|-----------------|-----------------|
| Mechanisms of action | Associated epilepsy syndromes | Anti-epileptic drugs |
| Voltage-gated ion channels | Sodium channels | GEFS | PHT, CBZ, TPM, LTG, OCBZ, FBMT, VPA, ZNS |
| Calcium channels | L-type | – | PB, FBMT |
| | P/Q type | AEA | LTG, OCBZ, LEV |
| | N-type | – | LTG, GBP, PG, ESM |
| | T-type | Absence | – |
| Potassium channels | Absence, ADLTL, EAT1-MK-PS | – |
| | K-4.1 | – | LEV, TPM |
| Ligand-gated ion channels | GABAa, receptor | JME, GEFS | PB, BZD, FBM, TPM, propofol CBZ |
| | Glutamate receptors | AMPA receptors | – | PB, TPM |
| | | NMDA receptors | – | FBMT |
| | | Kainate receptors | – | TPM |
| Synaptic vesicle proteins | SV2A | – | LEV, brivaracetam |
| Enzymes | GABA-transaminase | – | Vigabatrin |
| | Carbonic anhydrase | – | TPM, ZNS |
| GABA metabolism | Increase synthesis | – | VPA, GBP |
| | Decrease metabolism | – | VPA |
| | Prevent reuptake | – | TGB |

ADLTL = autodominant lateral temporal lobe epilepsy; ADNFLE = autosomal dominant nocturnal frontal lobe epilepsy; AEA = absence epilepsy with ataxia; CEZ = carbamazepine; EAT1-MK-PS = episodic ataxia type 1 with myokymia and partial seizures; ESM = ethosuximide; BZD = benzodiazepines; FBMT = felbamate; GBP = gabapentin; GE = generalized epilepsy; GEFS = generalized epilepsy with febrile seizures; HCN = hyperpolarization-activated cyclic nucleotide-gated cation; JME = juvenile myoclonic epilepsy; LEV = levetiracetam; OCBZ = oxcarbazepine; PB = phenobarbital; PHT = phenytoin; TGB = tiagabin; TPM = topiramate; VPA = valproic acid; ZNS = zonisamide.
zonisamide and lacosamide. Topiramate, as add-on and as monotherapy, was studied prospectively in a cohort of 47 patients with a brain tumour; 55.6% achieved seizure freedom and another 20% of the patients experienced a seizure reduction of >50% (Maschio et al., 2008). Novy et al. (2008) studied the effects of add-on and monotherapy with pregabalin in nine patients with a brain tumour. Fifty per cent of the patients became seizure free and 50% had a reduction in seizure frequency of >50%. Gabapentin was explored in a series of 14 patients and the authors reported that all patients had a reduction of >50% whereas 8 of 14 patients achieved seizure freedom (Perry and Sawka, 1996). The responder rate for zonisamide as add-on therapy was 83.3% (Maschio et al., 2009a). Lacosamide was studied in 14 patients with a mean follow-up of 5.4 months (Maschio et al., 2011). The responder rate to lacosamide was 78.6%. For the newer antiepileptic drugs: eslicarbazepine acetate, perampanel and retigabine, no studies in patients with a brain tumour have been performed.

A few studies have compared the efficacy of newer versus older antiepileptic drugs in the brain tumour population. In three studies, levetiracetam was compared to phenytoin (Milligan et al., 2008; Lim et al., 2009; Merrell et al., 2010). Two of the three were retrospective studies (Milligan et al., 2008; Merrell et al., 2010) that showed a similar efficacy in both groups. In the third, a prospective study, Lim et al. (2009) found that 75% of the eight patients treated with phenytoin were seizure free versus 87% of 15 patients on levetiracetam therapy. In one study, the efficacy of oxcarbazepine and traditional antiepileptic drugs was compared (Maschio et al., 2009b). The authors found a similar efficacy, but also showed that traditional antiepileptic drugs caused more side-effects. Finally, valproic acid and levetiracetam were compared as monotherapy or in combination with other antiepileptic drugs in a group of 140 patients (van Bremen et al., 2009). Seizure freedom was achieved in: 52% of patients using valproic acid, with or without other antiepileptic drugs; 59% of patients using valproic acid and levetiracetam with or without other antiepileptic drugs; 31% of patients using levetiracetam with or without other antiepileptic drugs; and 29% of patients treated with other (combinations of) antiepileptic drugs. Overall, in these studies, none of the antiepileptic drugs provided seizure freedom in all patients with a brain tumour.

Although large trials with antiepileptic drugs have been performed in the general epilepsy population, the same methodological flaws are met as in the brain tumour population, such as differences in target dosage between studies, designs that were primarily aimed at obtaining marketing licences instead of the best scientific evidence, bias in selection of patients, and short treatment duration. This might be illustrated by the fact that national guidelines regarding antiepileptic drugs treatment that were published between 2003 and 2006, such as the American Academy of Neurology guidelines, the UK National Institute for Health and Clinical Excellence (NICE) guidelines and the International League Against Epilepsy (ILAE) guidelines, are all based upon these large trials but differ in their recommendations (Perucca and Tomson, 2011). The American Academy of Neurology guidelines do not express any preferences among older and newer antiepileptic drugs, the UK NICE guidelines recommend the use of older antiepileptic drugs without a specific choice of agent and the ILAE guidelines recommend the use of phenytoin and carbamazepine as first line choices. Two large trials have been published since then. A large randomized double blind trial found similar effectiveness of levetiracetam and carbamazepine in patients with focal seizures (Brodie et al., 2007). The large randomized and controlled, but not double-blind standard and new antiepileptic drugs (SANAD) trial (Marson et al., 2007a, b) reported lamotrigine to be more effective than carbamazepine, oxcarbazepine, topiramate and gabapentin in patients with focal seizures, and valproic acid to be superior to lamotrigine and topiramate in generalized epilepsy. A comparison with this literature on patients with a brain tumour is difficult since research reports on antiepileptic drug treatment in the general epilepsy population are often restricted to populations with specific seizure types or epilepsy syndromes, while patients with a brain tumour are rarely stratified according to seizure type for study purposes.

Since many different types of antiepileptic drugs with similar efficacy exist, selection criteria to choose a specific antiepileptic drug in an individual patient are needed. The safety profile will play an important part in this decision. However, with a similar tolerability profile, specific selection criteria would be helpful. We investigated the correlation between the efficacy of levetiracetam in 34 patients with glioma and the expression of the synaptic vesicle protein (SV2A), the target of levetiracetam (de Groot et al., 2011). We found that the amount of SV2A expression in tumour and peritumoral tissue was a predictor for the efficacy of levetiracetam. Similar predictors for other antiepileptic drugs are not known (Kiniorns et al., 2006). In the future, identification of such predictors would be of great help in the choice of antiepileptic drugs for individual patients.

Since systemic treatment with antiepileptic drugs may induce many side-effects (see ‘Issues associated with antiepileptic drugs in patients with a brain tumour’ section), the possibility of focal drug treatment could be an interesting option. Focal treatment has been mainly investigated in animal models and methods include: intraparenchymal injection (bolus deposition), application via the epidural or subdural spaces, injection through a self-contained implanted device and convection-enhanced delivery. All these methods have a theoretical advantage over systemic therapy in that systemic side-effects are avoided, but there are many technical hurdles (Barcia and Gallego, 2009; Rogawski, 2009). The majority of clinical trials that use convection-enhanced delivery comprise small trials in patients with glioma (Rogawski, 2009). The reason is that patients with glioma are being operated on anyway with the epileptogenic focus coming within reach of the neurosurgeon. Thus far, the analysis of this technique for the treatment of focal epilepsy consists mainly of anticonvulsant toxins delivered locally in an experimental mouse model; this can produce long-lasting elevations in seizure threshold. The specific practical ways in which this technique should be used, however, have yet to be determined. Although some of these trials give promising results, optimal drug delivery may be achieved in only 20% of patients since there is often leakage into CSF subarachnoid spaces.
Issues associated with antiepileptic drugs in patients with a brain tumour

Adverse events

Since the targets of antiepileptic drugs are not solely present in the epileptogenic zone, antiepileptic drugs may cause a broad range of adverse events, such as liver dysfunction, drowsiness, bone-marrow suppression and skin rashes, etc (Gates, 2000). Patients with a brain tumour are more sensitive to the side-effects of antiepileptic drugs than other patients with epilepsy (Wen and Marks, 2002; Aguiar et al., 2004). For example, skin rash due to antiepileptic drugs (carbamazepine, phenobarbital and phenytoin) appears to occur more frequently in patients with brain tumours (Mamon et al., 1999). It has also been suggested that patients receiving radiotherapy and concomitant oxicarbapazepine have a higher risk of developing serious skin rashes such as Stevens–Johnson syndrome and toxic epidermal necrolysis (Maschio et al., 2010b).

The frequency (incidence) of adverse events differs considerably between antiepileptic drugs. Particularly, antiepileptic drugs of earlier generations show more adverse events (Klein et al., 2003). In addition to these potential adverse events, antiepileptic drugs frequently affect cognitive function. Deficits in cognitive functioning due to the tumour and anti-tumour treatment are a major concern in patients with a brain tumour (Douw et al., 2009), and the prescription of antiepileptic drugs to these patients will increase the risk for cognitive dysfunction. In the general epilepsy population, much research into the cognitive effects of antiepileptic drugs has been performed (Loring et al., 2007). Studies comparing the effect of antiepileptic drugs on cognition in healthy volunteers or in the epilepsy population showed that first generation antiepileptic drugs cause more cognitive side-effects than second generation antiepileptic drugs (Park and Kwon, 2008; Cavanna et al., 2010). Klein et al. (2003) found that patients with low-grade glioma who used antiepileptic drugs performed worse on cognitive tests than patients who did not use antiepileptic drugs. It needs to be emphasized that most patients in this study used first generation antiepileptic drugs. However, in another study a significant decline on the Mini-Mental State Examination in glioma patients using levetiracetam was shown (Maschio et al., 2010a), but this could also be attributed to tumour progression.

Moreover, seizure burden itself may negatively affect cognition (Motamedi and Meador, 2003; Carreno et al., 2008). Distinguishing seizure effects from antiepileptic drugs effects is very difficult, since antiepileptic drugs in patients with brain tumour are usually prescribed only to those patients who actually experienced seizures. However, it has been suggested that antiepileptic drug therapy rather than seizure burden affects cognitive function (Klein et al., 2003). Furthermore, cognitive deficits due to treatment with antiepileptic drugs have been described both in patients who are seizure free as well as in patients who are not seizure free (Hamed et al., 2009). As adverse events have a negative influence on the quality of life (Gilliam, 2002), choosing antiepileptic drugs with a lower chance of adverse events is preferable.

Drug–drug interactions

In general, the second generation antiepileptic drugs are less susceptible to pharmacokinetic interactions, a desirable characteristic for antiepileptic drugs that are prescribed to patients with glioma who are often subject to other medical treatment regimens. For that reason, the use of enzyme-inducing or enzyme-inhibiting antiepileptic drugs in patients with a brain tumour is discouraged. Levetiracetam is the optimal choice with regard to pharmacokinetic characteristics compared with other new antiepileptic drugs (topiramate, zonisamide, clonazepam, lamotrigine and ethosuximide) (Patsalos, 2000, 2002).

Recently, several studies have used first generation antiepileptic drugs to enhance chemotherapy due to their enzyme-inducing or -inhibiting properties. In a retrospective study, Oberndorfer et al. (2005) found that patients with glioblastoma on chemotherapy using enzyme-inhibiting antiepileptic drugs (valproic acid) had longer survival than patients using enzyme-inducing antiepileptic drugs; 13.8 versus 10.8 months, respectively. This finding was explained through the inhibition of P450 enzymes by valproic acid resulting in increased serum levels, and thus improved efficacy of chemotherapeutic agents and/or decreased serum levels with subsequent decreased efficacy of chemotherapeutic agents by enzyme-inducing antiepileptic drugs. In contrast to these findings, Jaeckle et al. (2009) prospectively showed that patients with glioblastoma receiving enzyme-inducing antiepileptic drugs had longer overall (12.3 versus 10.7 months) and progression-free survival (5.6 versus 4.8 months) than patients not receiving enzyme-inducing antiepileptic drugs. However, the results of this study could have been biased since only 2% of the patients used non-enzyme-inducing antiepileptic drugs. The mechanism behind these observations remains unclear and needs further investigation before definite conclusions can be drawn.

Apart from these indirect effects of antiepileptic drugs on survival, there are reports that several antiepileptic drugs might have intrinsic anti-tumour properties. Valproic acid inhibited tumour cell growth in in vitro and in vivo systems by modulating multiple pathways through its histone deacetylase inhibitor properties (Eyal et al., 2004; Li et al., 2005; Chavez-Blanco et al., 2006). Another study (Fu et al., 2010) showed that valproic acid induces autophagy in glioma cells. Autophagy is an alternative tumour suppressing mechanism to apoptosis. It is a caspase-independent process characterized by accumulation of autophagic vacuoles in the cytoplasm accompanied by an extensive degradation of organelles. Manipulation of this mechanism could provide support for anticancer therapy. Studies of valproic acid in combination with anti-tumour therapy in patients with glioma are ongoing (Phase II) (Blaheta et al., 2005; Duenas-Gonzalez et al., 2008). Other antiepileptic drugs, such as levetiracetam, have shown to restore the O6–methylguanine-DNA-methyltransferase inhibitory activity of mutated p53 activity in glioblastoma cell lines and thereby sensitizing glioblastoma cells to temozolomide (Bobustuc et al., 2010). O6–methylguanine-DNA-methyltransferase is a DNA repair protein and is associated with resistance to alkylating agents, such as temozolomide and lomustine (CCNU).
Pharmacoresistance

Pharmacoresistance or medically refractory epilepsy is common in patients with primary brain tumours, especially low-grade tumours. The ILAE Commission on Therapeutic Strategies defines refractory epilepsy as an epilepsy that is not controlled by two tolerated and appropriately chosen and used antiepileptic drugs schedules (whether as monotherapies or in combination) (Kwan et al., 2010). This definition is currently a matter of debate (Gomez-Alonso and Gil-Nagel, 2010).

Several hypotheses have been explored to explain drug pharmacoresistance that could also be applicable to pharmacoresistance in brain tumours. The first hypothesis, the target hypothesis (Remy and Beck, 2006), presumes alterations in drug targets; targets that antiepileptic drugs normally bind to are possibly altered in tumour and peritumoral tissue. Table 2 shows possible targets that are modified in patients with a brain tumour and the antiepileptic drugs that could bind to these targets. The second hypothesis is the transporter hypothesis (Kwan and Brodie, 2005; Loscher and Potschka, 2005): drugs can enter and leave the brain through carrier-mediated transport. Multi-drug transporters such as P-glycoprotein, multi-drug resistant protein and breast cancer resistance protein, and detoxifying enzymes such as glutathione-S-transferase π actively remove lipophilic molecules out of the brain parenchyma. This mechanism contributes to the function of the blood–brain barrier, which is to protect the brain from toxic substances. However, upregulation of multi-drug transporters, as may be found in epileptogenic brain tissue, may restrain access of antiepileptic drugs to the epileptogenic tissue (Schmidt and Loscher, 2005). Overexpression of multi-drug transporters, such as P-glycoprotein, multi-drug resistance protein and breast cancer resistance protein, has been reported in brain tumours and may underlie the drug refractoriness observed in patients with a brain tumour (Aronica et al., 2003, 2005; Decleves et al., 2006). In glioma, P-glycoprotein is highly expressed in endothelial cells of newly formed capillaries, and is not so extensive in the tumour cells themselves (Toth et al., 1996; Calatozzolo et al., 2005).

### Table 2 Molecular (or proposed) targets of known potential relevance to tumour associated epilepsy

<table>
<thead>
<tr>
<th>Target</th>
<th>Suggested relevance in (tumour type)</th>
<th>Location</th>
<th>Potential antiepileptic drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glutamate receptors changes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mGluR</td>
<td>GG, glioma</td>
<td>Tumour/peritumoral</td>
<td></td>
</tr>
<tr>
<td>AMPA receptors</td>
<td>GG</td>
<td>Tumour</td>
<td>PB, TPM</td>
</tr>
<tr>
<td>Kainate receptors</td>
<td>Astrocytoma</td>
<td>Peritumoral</td>
<td>TPM</td>
</tr>
<tr>
<td>NMDA receptors</td>
<td>GN</td>
<td>Tumour</td>
<td>FMT</td>
</tr>
<tr>
<td>GABA receptors</td>
<td>GG, glioma</td>
<td>Tumour</td>
<td>PB, BZD, FBM, TPM, propofol</td>
</tr>
<tr>
<td>Ion level changes</td>
<td>Fe²⁺</td>
<td>Glioma</td>
<td>Peritumoral (extracellular)</td>
</tr>
<tr>
<td></td>
<td>Mg²⁺</td>
<td>Glioma</td>
<td>Peritumoral (extracellular)</td>
</tr>
<tr>
<td></td>
<td>Ca²⁺</td>
<td>Glioma</td>
<td>Peritumoral (extracellular)</td>
</tr>
<tr>
<td></td>
<td>Na⁺</td>
<td>Glioma</td>
<td>Peritumoral (extracellular)</td>
</tr>
<tr>
<td>Voltage-gated ion channels</td>
<td>Sodium channels</td>
<td>Glioma</td>
<td>Tumour</td>
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<tr>
<td></td>
<td>Chloride channels</td>
<td></td>
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<tr>
<td></td>
<td>NKCC1</td>
<td>GG, glioma</td>
<td>Tumour, peritumoral</td>
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<tr>
<td></td>
<td>KCC2</td>
<td>GG, glioma</td>
<td>Tumour, peritumoral</td>
</tr>
<tr>
<td>Potassium channels</td>
<td>GG, glioma</td>
<td>Tumour</td>
<td></td>
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<tr>
<td>Inflammatory interleukines</td>
<td>IL-1β</td>
<td>GG</td>
<td>Tumour/peritumoral</td>
</tr>
<tr>
<td>Synaptic vesicle proteins</td>
<td>SV2A</td>
<td>GN, glioma</td>
<td>Tumour/peritumoral</td>
</tr>
<tr>
<td>Gap junctions (connexins)</td>
<td>CX32</td>
<td>GN, oligodendroglia</td>
<td>Tumour/peritumoral</td>
</tr>
<tr>
<td></td>
<td>CX34</td>
<td>GN, astrocytomas</td>
<td>Tumour/peritumoral</td>
</tr>
<tr>
<td>Enzym changes</td>
<td>Adenosine kinase</td>
<td>Glioma</td>
<td>Tumour/Peritumoral</td>
</tr>
<tr>
<td>Amino acids</td>
<td>Glutamate</td>
<td>Glioma</td>
<td>Peritumoral (extracellular)</td>
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<td>GABA</td>
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<td>Enzym changes</td>
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<td></td>
<td>PH changes</td>
<td>GN, glioma, meningeoma</td>
<td>Peritumoral</td>
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<tr>
<td></td>
<td>PI3K-mTOR pathway</td>
<td>GG, glioma</td>
<td>Tumour</td>
</tr>
</tbody>
</table>

BZD = benzodiazepines; CBZ = carbamazepine; FMT = felbamate; GBP = gabapentin; GG = ganglioglioma; GN = glioneuronal tumours; LEV = levetiracetam; LTG = lamotrigine; OCBZ = oxcarbazepine; PB = phenobarbital; PHT = phenytoin; TGB = tiagabine; TPM = topiramate; VPA = valproic acid; ZNS = zonisamide.

**Pharmacoresistance**

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high multi-drug resistance protein 1 expression has been reported both in tumour cells and in tumour vasculature of gliomas (Calatozzolo et al., 2005).

Expression of these transporters (breast cancer resistance protein, P-glycoprotein and multi-drug resistance protein 1) has also been reported in glioneuronal tumours (Aronica et al., 2003, 2005). The overexpression of multi-drug resistant proteins can be intrinsic or acquired, meaning that the resistance is either present before exposure to antiepileptic drugs, resulting in immediate resistance or develops during treatment, resulting in tolerance to antiepileptic drugs (Loscher and Potschka, 2005). In addition, it has been hypothesized that so-called cancer stem-like cells in glioblastoma multiforme express breast cancer resistance protein and play a role in therapy resistance and tumour recurrence (Bleau et al., 2009). Metastatic brain tumours differ in this aspect from primary brain tumours. The neovasculature of secondary brain tumours express characteristics of the blood vessels of the primary tumour, with subsequent altered characteristics of the blood–brain barrier (Gerstner and Fine, 2007). For instance, melanoma metastases express only 5% of the P-glycoprotein level normally found in the blood–brain barrier and non-small cellular lung carcinoma metastases only 30–40% (Gerstner and Fine, 2007). This suggests pharmacoresistance via an enhanced expression/function of multi-drug transporters is less of a problem in metastatic brain tumours.

In order to support the theory of the transporter hypothesis in pharmacoresistance in patients with a brain tumour, the antiepileptic drugs must be substrates for these transporters. One study found no measurable directional transport of antiepileptic drugs (phenytoin, carbamazepine and levetiracetam) by human P-glycoprotein or multi-drug resistance protein 2 (Baltes et al., 2008). Recently, the same research group used a different assay to determine the transport of antiepileptic drugs and found that several major antiepileptic drugs (phenytoin, phenobarbital, lamotrigine and levetiracetam, but not carbamazepine) are transported by P-glycoprotein (Luna-Tortos et al., 2008). Even the newer drug levetiracetam, which has long been thought not to be a P-glycoprotein substrate, was shown to be a weak substrate for P-glycoprotein (Luna-Tortos et al., 2008). As far as multi-drug resistance proteins 1, 2 and 5 are concerned, carbamazepine, valproic acid, levetiracetam, phenytoin, lamotrigine and phenobarbital were not substrates (Luna-Tortos et al., 2010). Correlations between drug efficacy and expression of multi-drug transporters have been reported for both animals and humans (Rizzi et al., 2002; Marchi et al., 2005; van Vliet et al., 2007). The upregulation of multi-drug transporters in the vasculature of primary brain tumours and the fact that the majority of antiepileptic drugs are substrates for multi-drug transporters, suggest that multi-drug transporters have a role in pharmacoresistant epilepsy in patients with a brain tumour.

The third hypothesis is the intrinsic severity hypothesis (Rogawski and Johnson, 2008). This model suggests that neurobiological factors, which underlie disease severity, contribute pharmacoresistance. It is based on the observation that patients with high seizure frequency in the early phase of epilepsy have a poor outcome of pharmacotherapy. In other words, differences in inherent epilepsy severity have influence on an individual patient’s response to treatment. This is comparable to other diseases, which often vary from mild to severe and also vary in response to treatment.

**Current state: treatment of the tumour**

**Surgery**

Surgery focuses on resection of the tumour as radically as possible in order to delay tumour growth and lengthen survival (Smith et al., 2008). The extent of resection of the tumour is limited by functional areas of the brain. Further, removal of the tumour may also lead to reduction of seizures, and many patients are seizure free after oncological surgery (Chang et al., 2008).

It is important to note that the percentage of patients with a significant reduction in seizures after surgery is higher when more sophisticated surgical techniques are applied. With conventional oncological surgery the epileptogenic zone is not always resected, since this zone is often not restricted to the tumour area. In fact, in one-third of patients the tumour area is not the epileptogenic zone (Gilmore et al., 1994). With the help of imaging techniques that are routinely applied in epilepsy surgery in non-tumour patients, the epileptogenic zone can be identified and exactly localized. These imaging techniques are functional MRI, Wada test, magnetoencephalography, diffusion tensor imaging, interictal electrocorticography and electrostimulation during awake craniotomy. Subsequently, simultaneous resection of both the tumour and (if possible) the epileptic focus provides a significantly better control of seizures than oncological surgery alone. The percentage of patients with oncological surgery alone that achieve seizure freedom ranges from 65% to 77% (Choi et al., 2004; Chang et al., 2008), whereas that percentage ranges from 82% to 92% after extended lesionectomy (Lombardi et al., 1997; Duffau et al., 2002; Zaatreh et al., 2003; Bauer et al., 2007).

Thus, while having to decide whether oncological surgery is necessary, epilepsy surgery should always be taken into consideration. This is especially so in patients with low-grade (WHO grades I and II) gliomas, without neurological deficits and low risk for progression or dedifferentiation, and when epilepsy constitutes the only symptom, surgery should be considered (Iannelli et al., 2000). This is, however, a constant issue of debate (Langfitt et al., 2007; Teixidor et al., 2007; Chang et al., 2008; Sanai and Berger, 2008), since surgery comes with many risks, and may even increase seizure frequency. Apart from that, for epilepsy surgery the identification of the epileptogenic zone is pivotal and the required diagnostic work-up may consume a considerable amount of time, which may be undesirable in the case of a malignant brain tumour.

Thus, although we advocate considering the application of an epilepsy surgery strategy in every patient with a brain tumour suffering from seizure, whether this strategy should be followed eventually depends on: (i) the grade and prognosis of the tumour (the higher the tumour grade, the faster or more restricted the work-up and this might even be impossible); (ii) the localization of
the tumour (the more difficult to achieve gross total or subtotal resection, the more elaborate the work-up if there is a considerable chance that this will improve resectability); and (iii) the severity of epilepsy if tumour surgery should be combined with epilepsy surgery (the more refractory the epilepsy is, the lower the chance that a patient becomes seizure free postoperatively).

The latter would imply that pre-surgical evaluation includes functional MRI, magnetoeencephalography etc. in order to enable the patient and the physician to make a reasoned decision regarding both the risks of surgery as well as the chances of seizure freedom. If there is an urgent oncological reason for intervention—for example in case of a rapidly growing high-grade glioma—a full work-up for epilepsy surgery is undesirable due to the fact that it delays surgical treatment. For patients in the inbetween grey area, informed consent must be the defining feature—the potential benefits of completing full pre-surgical epilepsy evaluation weighed up against the theoretical risks of delaying surgical treatment in that individual. Important considerations in planning surgical treatment in patients with glioma are variables that predict seizure freedom and show a requirement for pre-surgical evaluation for epilepsy surgery. For example, duration of seizures of <1 year predicts a good outcome after surgery whereas medically refractory epilepsy and simple partial seizures predict a bad outcome after surgery in patients with a brain tumour (Englot et al., 2011). This supports the integration of the epileptologist as early as possible in the decision process.

Radiotherapy and chemotherapy

Radiotherapy and chemotherapy are frequently applied in the treatment of patients with a brain tumour in order to prolong survival or improve quality of life. Although seizure reduction is not the first priority of chemotherapeutic agents, these therapies also have an effect on seizure occurrence. Few studies have addressed this issue. In a small study in five patients with a brain tumour receiving cranial irradiation, 90% reduction in seizure frequency was found in three patients and 75% reduction in seizure frequency in one patient (Rogers et al., 1993). In another small study of nine patients with a brain tumour, five patients achieved seizure freedom and four patients reported a reduction of >75% in seizure frequency (Chalifoux and Elisevich, 1996). Stereotactic radiosurgery with gamma knife resulted in 13 of 24 patients with seizure control (Schrottner et al., 1998; Quigg and Barbaro, 2008).

Regarding chemotherapy, a few studies suggest a role of temozolomide and the combination of procarbazine, vincristine and CCNU (lomustine) (PCV scheme) in reducing seizure frequency (Brada et al., 2003; Pace et al., 2003). Recently, a cohort study compared the seizure frequency of 39 patients with low-grade glioma treated with temozolomide to 30 patients with low-grade patients under observation (and not receiving any form of post-operative chemotherapy) (Sherman et al., 2011). There was a significant difference in reduced seizure frequency between the two groups: 59% of the patients using temozolomide and 13% of patients not using temozolomide showed a reduction of >50%. These findings suggest that chemotherapy and radiotherapy might decrease epilepsy burden significantly. However, larger prospective studies are needed.

Clinical impact

Treatment of seizures in patients with a brain tumour is complex and often unsuccessful. Although antiepileptic drugs have many different modes of action, none of these seem to effectively modify the epileptogenic nature of brain tumours (Schaller and Ruegg, 2003). In order to develop more effective therapies without adverse events, it is essential to return to the key question, why do brain tumours cause epilepsy?

Pathophysiology of tumour-related epilepsy: what makes brain tumours epileptogenic?

Epilepsy commonly develops in patients with a brain lesion, but not all patients with a brain lesion suffer from epilepsy. Tumour-associated epilepsy can be classified under ‘symptomatic epilepsy’, which is defined as ‘the development of epilepsy caused by an identifiable injury or lesion’ (Hauser, 1997). Lesions or injuries such as stroke, contusions, abscesses, vascular malformations and malformations of cortical development, may all trigger a succession of events that sets off epilepsy. However, the cellular mechanisms underlying the epileptogenesis of those lesions are not clear. Given the fact that both intracerebral and extracerebral tumours can cause epilepsy and differences in seizure frequency exist between tumours of the same histopathological tumour type, it is likely that in tumour-related epilepsy multiple mechanisms are involved, including tumour-related factors (histological type, location), environment-related factors and functional changes (Fig. 1).

Although any tumour type can cause seizures, low-grade tumours are more frequently associated with epilepsy than high-grade tumours (van Breemen et al., 2007). High-grade tumours that present with seizures are usually smaller in size than high-grade tumours that present with other symptoms such as focal neurological deficits. In contrast, low-grade tumours that present with epilepsy are usually larger tumours than the tumours without epilepsy (Lee et al., 2010). This suggests that the slow growth rate allows time to develop functional changes. Patients with temporal or frontal located low-grade tumours, are more likely to present with seizures or develop seizures during the course of their disease (Sirven et al., 2004; van Breemen et al., 2007) than patients with deeply located tumours (e.g. pericallosal region). Also, patients with tumours in the insular cortex are more likely to present with seizures (Lee et al., 2010). In temporal lobe epilepsy, the insular region is associated with seizure spread. This could implicate that tumours located near or in the cortex are more likely to affect neuronal tissue and thus present with seizures.

Tumours also share a number of similar histopathological features suggesting that a common set of primary mechanisms of epileptogenesis could predominate. Some tumours consist of a mixture of dysplastic neurons and neoplastic glial cell (e.g. ganglioglioma), while others display neoplastic glial cells (e.g. astrocytes and oligodendrocytes). Cellular composition and neurochemical profile of glioneuronal tumours may be relevant for epileptogenesis (e.g. the presence of a hyperexcitable neuronal component).
Possibly, more neuronal involvement is associated with epileptogenicity. On the other hand, an astrocytic basis for epilepsy has been proposed previously (Boison, 2010), since astrocytes support neuronal synapses and contribute to the regulation of neurotransmission.

A number of other hypotheses regarding pathophysiology have been put forward, such as blood–brain barrier disruption, pH imbalance and metabolic changes due to vascular disturbance and hypoxia. Such hypotheses have been previously summarized by Beaumont and Whittle (2000), Schaller and Ruegg (2003) and Shamji et al. (2009). In this review, specific aspects of epileptogenesis in patients with a brain tumour are discussed. These include neurotransmitter and receptor expression, since these alterations may provide targets for drug therapy, but also genetic seizure susceptibility. Tumour growth not only leads to structural changes, but also to functional changes of tumour cells and the surrounding tissue. Brain tumour tissue and the peritumoral tissue are both known to express altered levels of receptors and neurotransmitters. However, it is generally thought that the peritumoral tissue and the epileptogenic properties of the surrounding brain tissue; and (iii) what is the effect of the tumour on brain networks? All three questions begin with the tumour and all three have clinical implications, both for surgical approaches and for antiepileptic drug therapy.

**What happens in the tumour?**

For glioneuronal tumours, several studies have suggested an intrinsic epileptogenicity, indicating the presence of a hyperexcitable neuronal component. Electroencephalographic studies show that epileptiform activity is associated with a high neuronal density within the lesion (Ferrier et al., 2006). Regarding tumours of glial origin, abrupt tissue damage leading to necrosis and haemosiderin deposition and to oedema has been proposed as pathophysiological factor within the tumour (Riva, 2005). This theory is mainly applicable to high-grade glioma. Low-grade tumours are thought to slowly cause functional changes. These changes can be subdivided in categories used below.

**Gap junctions**

One hypothesis is that a disturbed communication between cells contributes to epileptogenesis. Intercellular communication
between glial cells takes place through gap junction channels: connexins. Low-grade gliomas demonstrate overexpression of connexin 43 both in the tumour as well as in the peritumoral cortex, and oligodendroglioma and glioneuronal tumours show overexpression of connexin 32 (Aronica et al., 2001a).

Voltage-gated ion channels and transporters
Experimental data in vitro and in vivo have shown a high density of voltage-gated sodium channels in tumour cells (Patt et al., 1996; Labrakakis et al., 1997) suggesting that tumour cells can generate action potentials. Increase of the sodium–potassium chloride cotransporter (NKCC1) expression and reduced expression of the potassium–chlordie cotransporter (KCC2) has also been reported in glioneuronal tumours (Aronica et al., 2007a, 2008). The dysregulation of these transporters can contribute to epileptogenicity in ganglioglioma by modulation of GABA receptors (Yamada et al., 2004).

Receptor and synaptic vesicle changes
Dysplastic glial cells in glioma also express compounds normally not present in glial cells, such as synaptic vesicle proteins (De Groot et al., 2010). The function of these proteins is not understood, but they might play a role in epileptogenesis. Glioma tumour cells express synaptic vesicle protein 2A (SV2A) (De Groot et al., 2010). Dysfunction of SV2A leads to calcium accumulation during repeated action potential generation and might play an important role in epileptogenesis. Both gliomas and gangliogliomas express specific glutamate receptor subtypes including both ionotropic and metabotropic receptors (Aronica et al., 2001b; Maas et al., 2001; Samadani et al., 2007). This implies a specific role of glutamatergic neurotransmission in the epileptogenicity of these lesions. In glioblastoma, a downregulation and mislocalization of AMPA receptors compared to normal non-neoplastic brain and low-grade gliomas was reported, suggesting that downregulation of ionotropic glutamate receptors in a glutamate rich environment allows glioblastoma to be less excitable than low-grade tumours (van Vuurden et al., 2009). Also, a decreased expression of glial glutamate transporters has been found that may increase extracellular glutamate resulting in high excitability (Samadani et al., 2007; de Groot and Sontheimer, 2010). A downregulation of several GABAa receptor subunits (α1, α5, β1, β3 and δ) was detected in ganglioglioma suggesting an impairment in inhibitory neurotransmission (Samadani et al., 2007; Aronica et al., 2008).

Genetics and molecular pathways
Low expression of potassium channel genes has been found in ganglioglioma indicating a disturbed ion homeostasis that could lead to epilepsy (Aronica et al., 2008). The leucine-rich, glioma inactivated gene 1 (LGI1) is a possible tumour suppressor gene of glioma and mutations in this gene are associated with autosomal dominant lateral temporal lobe epilepsy (Gu et al., 2005). Low expression of leucine-rich, glioma inactivated gene 1 in glioma tissue has been observed, suggesting a role for this gene in the epileptogenesis (Gu et al., 2005). In ganglioglioma, several components of the phosphatidylinositol-3 kinase mammalian target of rapamycin (PI3K-mTOR) signalling pathways are activated (Boer et al., 2010). Activation of this pathway might contribute to epileptogenesis and is a potential target for mTOR inhibitors, such as rapamycin (Zeng et al., 2008). In glioblastoma and low-grade glioma, the pi3K-mTOR pathway plays a role in the development of the tumours (McBride et al., 2010; Sunayama et al., 2010), suggesting common genetic pathways for tumour-associated epilepsy and glioma (Berntsson et al., 2009).

Glutamate hypothesis
Calcium (Ca^{2+}) permeable AMPA receptors are activated due to glutamatergic stimulation in high-grade glioma. The transport of glutamate through Na^{+} dependent glutamate uptake is almost absent in glioma, leading to excess amounts of glutamate. Furthermore, gliomas use the x_{c}^{-} cystine glutamate system. It transports cystine in the cell and, in exchange, glutamate is released. The high glutamate release and low uptake suggest overactivation of neuronal glutamate receptors. Excessive amounts of glutamate also lead to excitotoxicity and cellular oedema, subsequently leading to seizures (de Groot and Sontheimer, 2010).

What is the influence of brain tumours on the peritumoral area?
The epileptogenicity of the peritumoral zone is supported by findings of functional and immunocytochemical studies. These studies show network alterations and reveal cytoarchitectural and neurochemical changes in the perilesional cortex resected from patients with epilepsy associated with different types of focal brain lesions, including glial tumours (Goel et al., 2003; Shamji et al., 2009). It is likely that peritumoral cells (both neuronal and glial) have a distorted function. Rapidly progressive tumours infiltrate neighbouring tissue, resulting in excitability (Kohling et al., 2006). Peritumoral neurons show downregulation of inhibitory synapses and upregulation of excitatory synapses (McNamara, 1999) and demonstrate abnormal electrophysiologic properties (Steriade and Amzica, 1999). Peritumoral ischaemia (mainly induced by high-grade tumours) could play a role in epileptogenesis, but does not explain why low-grade tumours more frequently present with seizures than high-grade tumours. Low-grade tumours cause chronic functional changes in peritumoral cortex more often than high-grade tumours. These changes can be subdivided into the following categories.

Gap junctions
Alterations in gap-junctions (connexins) have been observed in the peritumoral tissue of both glial and glioneuronal tumours (Aronica et al., 2001a).

Voltage-gated ion channels and transporters
Peritumoral tissue of patients with glioma and epilepsy show an increased expression of NKCC1 and a modest expression of KCC2 compared to non-epileptic control tissue (Conti et al., 2011). It has been shown that altered neuronal expression of NKCC1 and KCC2 in peritumoral tissue of glial tumours leads to a positive shift of E_{GABA} (depolarized reversal potential) (Conti et al., 2011). This might lead to an inhibition of GABAergic function.
Receptor changes
Peritumoral astrocytes express an increased amount of kainate receptors (Aronica et al., 2001b). These receptors downregulate GABAergic inhibition and may predispose to epilepsy. Furthermore, multiple metabotropic glutamate receptors are overexpressed in the peritumoral cortex (Aronica et al., 2001b).

Ion level changes
Macro- or microhaemorrhage may lead to injury to the neuronal membrane resulting in higher peritumoral extracellular levels of iron (Fe^{3+}) (Shamji et al., 2009), which may change the membrane potential of neurons. Extracellular ion level changes are also reported for magnesium (Mg^{2+}) and calcium (Ca^{2+}), probably released from oedema and haemorrhage. Decreased extracellular levels of magnesium (Mg^{2+}) lead to spontaneous epileptiform discharges (Schaller and Ruegg, 2003).

Amino acids
Extracellular amino acid changes have also been reported in peritumoral tissue. Higher levels of extracellular glutamate have been found in peritumoral brain parenchyma of tumour patients with epilepsy compared to non-tumour patients with epilepsy (de Groot and Sontheimer, 2010). Abnormal levels of glutamate can result in higher neuronal excitability. Several studies have shown alterations in the levels of GABA, but the studies are contrasting. One study reports a higher level of GABA, while the other reports a lower level of GABA (Beaumont and Whittle, 2000; Shamji et al., 2009). Altered concentrations of other amino acids have also been shown, though the pathological significance remains unclear.

Enzyme changes
Enzymatic changes have been demonstrated in peritumoral tissue (Shamji et al., 2009). These changes may impair neurotransmitter synthesis and storage leading to alterations in signalling, processing and neuronal excitation.

Inflammation
An epileptogenic role has also been suggested for inflammation (Vezzani and Granata, 2005; Vezzani et al., 2011). Brain tumours often show a prominent immune response. Upregulation of inflammatory interleukins (such as IL-1β) in ganglioglioma, have been suggested to play a role in epileptogenicity (Aronica et al., 2008; Vezzani et al., 2011). Inflammation activates a cascade of proinflammatory cytokines and induces alterations in the blood-brain barrier possibly leading to epilepsy.

What is the effect of brain tumours on the whole brain (brain networks)?
The human brain can be interpreted as a highly complex neural network. In order to function properly, a network requires several concepts such as segregation and integration. It has been proposed by Watts and Strogatz (1998) that an optimal network holds a balance between these characteristics and may be described as a ‘small-world’ network. The features of small-world networks are—at least partly—genetically determined (Smit et al., 2008). Functional connectivity is a measure that is used to express the degree of communication between brain areas and one of the parameters that are used to describe networks (Rejneveld et al., 2007). Brain tumours are thought to disrupt functional connectivity, thus interfering with normal brain function. Dysfunctional tissue disturbs dynamic interactions that normally occur between intact brain areas and therefore causes changes in connectivity. Magnetoencephalography studies demonstrate altered functional connectivity in patients with a brain tumour compared to healthy controls (e.g. low-frequency theta band connectivity is increased and the small-world configuration is disturbed) (Bartolomei et al., 2006). Loss of functional connectivity in patients with a brain tumour affects not only the tumour area, but also other brain areas (Bartolomei et al., 2006). The mechanisms underlying the alteration of functional connectivity are unclear.

Studies in patients with temporal lobe epilepsy suggest that the small-world configuration is more disrupted in patients with a longer history of seizures (van Dellen et al., 2009). Moreover, in patients with epilepsy, increased connectivity has been reported (Douw et al., 2010a), and patients with a brain tumour with more severe epilepsy (higher number of seizures) display a stronger increase of functional connectivity in the theta band (Douw et al., 2010b). This suggests that alterations in functional connectivity can contribute to tumour-related epilepsy.

Both structural changes and functional deficits caused by the tumour have been proposed to alter functional connectivity. It has been shown that changes in membrane ion permeability directly lead to changes in functional network properties. For instance, blockade of GABA receptors alters theta band activity (Mackenzie et al., 2002). In an in vitro model of stroke-induced epilepsy, glutamate-injured hippocampal neuronal networks had a more random network topology than non-injured neuronal networks, and became hyperexcitable (Srinivas et al., 2007). In another study it has been demonstrated that dysfunction of the inhibitory GABAergic neuronal network and a reduced number of inhibitory interneurons in perilesional tissue surrounding low-grade glioma contribute to the generation and propagation of epileptic seizures through the induction of abnormally functioning neuronal networks in these highly epileptogenic lesions (Aronica et al., 2007b).

As mentioned before, not only neurons but also astrocytes surrounding the lesion undergo reorganization (Hatten et al., 1991; Landis, 1994; Norenberg, 1994; Zhang and Olsson, 1995). Increased coupling between astrocytes in perilesional tissue of patients with low-grade glioma with epilepsy reflected by connexin 43 (Aronica et al., 2001a), is thought to contribute to the (local) hypersynchronization of neuronal firing at the epileptic focus (Lee et al., 1995; O’Connor et al., 1998). Gap junctions may also play a role in synchronizing neocortical networks and may lead to characteristic neocortical firing patterns in focal cortical dysplasias (Gigout et al., 2006). Recently, increased expression of lynx1 protein has been identified to prevent plasticity in the visual cortex in adults (Morishita et al., 2010). Removal of this protein led to enhanced signalling of nicotinic acetylcholine receptors. This suggests that the stability of cortical networks can be modulated by proteins.

Taken together, these findings suggest that (peri-)lesional changes may induce alterations in local neuronal network
topological features. We suggest that a focal lesion leads to local imbalance between inhibition and excitation at the receptor, neuronal and astrocytic level. This causes brain networks to be disorganized. Eventually, patients develop seizures. However, structural changes and cellular deficits might not necessarily lead to affection of networks, and other, until now unknown factors, might contribute to epileptogenesis.

**Future directions**

As of now, treatment of epilepsy in patients with a brain tumour is far from optimal. Considering the impact of the tumour on peritumoral tissue and neural networks regarding epileptogenesis, therapy should primarily be targeted at the focal lesion. The foremost step is eliminating the tumour and the epileptic focus, combining oncological and epilepsy surgery techniques, and—if appropriate—postoperative chemo- and radiotherapy. Future research should aim at further characterization of the impact of surgical resection on epileptogenic brain networks. Correlations between specific neurosurgical interventions on the one hand and network alterations and changes in seizure frequency on the other hand should be assessed in detail. This will eventually result in more insight in the effects of surgical resection on network changes and seizure outcome, in this way making neurosurgical intervention a more effective antiepileptic treatment in patients with a brain tumour. Further studies assessing the effects of postoperative anti-tumour therapy on seizure frequency are also needed before postoperative anti-tumour therapy becomes a routine part of modern antiepileptic treatment.

If the optimization of treatment of the tumour does not result in appropriate seizure reduction, treatment with antiepileptic drugs should be the next step. However, many processes that are associated with tumour-related epilepsy are not adequately targeted by the current antiepileptic drugs. This discrepancy may explain the limited success of many antiepileptic drugs in epilepsy patients with a brain tumour (Shamji et al., 2009). Future research should be aimed at the identification of receptors and neurotransmitters that attribute to tumour-related epilepsy. Subsequently, existing drugs could be re-evaluated or new drugs could be developed that specifically act on these targets. Possible factors predicting efficacy and tolerability should also be evaluated in order to facilitate the choice of antiepileptic drugs, and to define strategies overcoming drug resistant proteins, which might further improve antiepileptic drug treatment.

**Conclusion**

Brain tumours often cause epilepsy and therapy is far from perfect. Epileptogenesis is not well understood, but presumably comprises structural and cellular/molecular changes induced by the tumour that leads to changes in the surrounding tissue and at further distance, eventually resulting in alterations in functional connectivity. Therapy should aim at eliminating the epileptic focus and decrease epileptic activity of the focus. Research is warranted both for optimizing anti-tumour treatment and its effects on epilepsy and for elucidation of the underlying pathophysiology of tumour-related epilepsy to provide targets for new therapies.

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