Invited review

Tonic GABA$_A$ receptor-mediated signalling in temporal lobe epilepsy

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ABSTRACT

The tonic activation of extrasynaptic GABA$_A$ receptors by extracellular GABA provides a powerful means of regulating neuronal excitability. A consistent finding from studies that have used various models of temporal lobe epilepsy is that tonic GABA$_A$ receptor-mediated conductances are largely preserved in epileptic brain (in contrast to synaptic inhibition which is often reduced). Tonic inhibition is therefore an attractive target for antiepileptic drugs. However, the network consequences of a commonly used approach to augment tonic GABA$_A$ receptor-mediated conductances by global manipulation of extracellular GABA are difficult to predict without understanding how epileptogenesis alters the pharmacology and GABA sensitivity of tonic inhibition, and how manipulation of tonic conductances modulates the output of individual neurons. Here we review the current literature on epilepsy-associated changes in tonic GABA$_A$ receptor-mediated signalling, and speculate about possible effects they have at the network level.

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1. Introduction

Alterations in inhibition have often been suggested to underpin the development of epilepsy or the propensity of a brain to have seizures. Indeed, it is not unusual to see epilepsy and the development of epilepsy (epileptogenesis) illustrated as a balance of inhibition and excitation tipping towards excitation and away from inhibition. However, there is gathering evidence that this view is a vast oversimplification. Not least, the observation that untreated animals and humans with epilepsy will often have infrequent seizures indicates that any tip of the balance must be compensated, but compensated in a fashion that generates a less stable network. Although most studies have investigated changes in fast, synaptic inhibition mediated by the synaptic release of GABA onto postsynaptic GABA$_A$ receptors (GABA$_A$Rs), there has been a burgeoning interest in the possible role of the effects of extracellular GABA on high affinity, slowly desensitizing extrasynaptic GABA$_A$Rs, often termed "tonic inhibition".

The diffuse action of GABA through activation of extrasynaptic GABA$_A$Rs has long been recognized as an important signalling mechanism in the peripheral nervous system (Brown, 1979). It was even postulated that, in the absence of vesicular neurotransmitter release, GABA can modulate the excitability of unmyelinated fibres

through transporter-mediated efflux from glial cells in sympathetic ganglia (Bowery et al., 1976). Extra- and perisynaptic GABA$_A$Rs are also abundant in the central nervous system (DeBlas et al., 1988; Somogyi et al., 1989; Nusser et al., 1996, 1998). It was not until mid 90-s, however, that the presence of the tonic GABA$_A$R-mediated currents was documented in the central nervous system (Otis et al., 1991; Salin and Prince, 1996; Brickley et al., 1996). Not only were such currents determined in different cell populations, but also their functional role as a mechanism of reducing cell excitability was recognised (Brickley et al., 1996). Since then, this form of GABAergic signalling through persistently active GABA$_A$Rs has attracted considerable attention and has been described in many brain regions ranging from cortical areas to subcortical structures (for reviews see: Semyanov et al., 2004; Mody and Pearce, 2004; Farrant and Nusser, 2005). Being a powerful mechanism regulating neuronal output, it has been implicated in a variety of cognitive processes during normal brain function and has been demonstrated to be involved in the pathophysiology of several neurological disorders (Curia et al., 2009; Cope et al., 2009; Clarkson et al., 2010). Of particular interest in this respect is the role of tonic inhibition in restraining excessive excitation in epilepsy (e.g. Maguire et al., 2005). The potential importance of tonic inhibition in human epilepsy has been emphasized through the observation that polymorphisms and mutations in genes encoding extrasynaptic GABA$_A$Rs are associated with several human epilepsies (Dibbens et al., 2004; Feng et al., 2006; Eugène et al., 2007), implying that deficits in tonic GABA$_A$R-mediated signalling have

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deleterious effects on network behaviour. The significance of tonic inhibition for maintaining normal neuronal and network function is further underscored by the finding that mouse mutants lacking extrasynaptic GABA$_A$Rs that mediate tonic conductances in the cerebellum compensate by up-regulating the two-pore-domain K$^+$ channel inhibitory conductance. This compensatory mechanism results in neurons in the knockout mice having an unaltered response to excitatory synaptic inputs (Brickley et al., 2001). Conversely, tonic inhibition itself may substitute for the loss of other membrane conductances (e.g. HCN-mediated conductance) involved in the regulation of cell excitability (Chen et al., 2010).

However, determining the role of tonically active GABA$_A$Rs in epilepsy is not trivial. Although there have been advances in our understanding of the effects of tonic GABA$_A$R-mediated conductances on elementary neuronal computations, how these translate into network behaviour remains poorly understood. In epilepsy, the situation is further complicated by cell loss, alterations in intrinsic cell excitability and changes in network connectivity. Here we review the current developments in the field and the emerging picture, which, unfortunately, is still far from being complete. Due to the space limitations we will only focus on the changes that are related to temporal lobe epilepsy.

2. Tonic inhibition in epilepsy

Epilepsy is a disorder characterised by recurrent paroxysms of excessive network activity. Although multiple mechanisms (such as changes in intrinsic neuronal properties, formation of excitatory recurrent connections, neuronal degeneration, etc.) may be involved in the generation of pathological network activity, there is strong evidence that dysfunction of GABAergic signalling plays a critical role in the pathogenesis of epilepsy and the generation of seizures. Studies using in vitro models of epilepsy in acute rodent slices have highlighted the importance of feed-forward inhibition in restraining excitatory drive, so that a breakdown of inhibition is necessary for seizure propagation (Trevelyan et al., 2006, 2007). There have been complementary findings in brain slices from humans with epilepsy, in which loss of GABAergic inhibition is observed prior to a seizure (Huberfeld et al., 2011). It is therefore not surprising that loss of functional inhibition has been linked to epileptogenesis. Depending on the aetiology this is generally (although not universally) seen as a loss of interneurons and/or reduction of the number of the GABAergic synapses on surviving principal neurons (Cossart et al., 2001; Wittner, 2001; Buckmaster et al., 2002; Kobayashi and Buckmaster, 2003; Shao and Dudek, 2005; Hunt et al., 2009; Wyeth et al., 2010). Morphological and functional changes in the hippocampal formation rapidly follow the epileptogenic insult and may continue for an extended period of time up to several months or even longer (Sloviter, 1991; Friedman et al., 1994; Leroy et al., 2004; Pavlov et al., 2011a). Despite many adaptive and compensatory processes in epileptic tissue the general consensus is that the net outcome of these changes is the loss of phasic (synaptic) inhibition.

Correlation between the magnitude of tonic and phasic inhibition in hippocampal neurons suggests that vesicular GABA release is an important source of extracellular GABA (Glykys and Mody, 2007). Therefore, loss of interneurons and/or a reduced number of GABAergic synapses would be expected to result in an overall decrease in GABA release, a reduced concentration of GABA in the extracellular space, and consequently a reduction in tonic inhibition. However, experimental evidence indicates that, in post-status epilepticus animals (during and beyond the epileptogenic period), tonic GABA$_A$R-mediated currents are maintained in many hippocampal neurons including CA1 pyramidal cells, stratum radiatum interneurons and dentate granule cells (Scimemi et al., 2005; Zhang et al.,

2007; Goodkin et al., 2008; Rajasekaran et al., 2010). Some studies have even reported increased tonic inhibition (Scimemi et al., 2005; Naylor et al., 2005; Zhan and Nadler, 2009). Similar results have been obtained in models of post-traumatic epilepsy that often display hippocampal pathology and can result in temporal lobe seizures (D'Ambrosio et al., 2005; Kharatishvili et al., 2006; Swartz et al., 2006). Unaltered tonic inhibition has been reported in dentate granule cells following lateral fluid-percussion brain injury (Pavlov et al., 2011a), or tonic inhibition has been shown to be enhanced after controlled cortical impact (Mtchedlishvili et al., 2010). Although there is no control comparator, large tonic GABA$_A$R-mediated currents are also present in neocortical and dentate neurons from humans with temporal lobe epilepsy (Scimemi et al., 2006).

Preservation of tonic GABA$_A$R-mediated conductances in the hippocampus proper and dentate gyrus is, therefore, a consistent finding in tissue from epileptic animals/humans [but see (Qi et al., 2006) for an in vitro neuronal culture model of epileptiform activity], which makes tonic inhibition an attractive target for anticonvulsant drugs. However, several questions need to be addressed in order to turn this treatment approach into an effective pharmacological tool. How are tonic conductances maintained in epilepsy in the face of decreased phasic inhibition? Are these tonic currents mediated by the same GABA$_A$R subtypes as in control tissue and, therefore, retain their pharmacology? Is GABA uptake altered in epilepsy? What are the network effects of altering tonic inhibition in interneurons and pyramidal cells?

3. GABA$_A$ receptor plasticity

Epileptogenesis is associated with changes in the expression of various GABA$_A$R subunits in animal models (e.g. Brooks-Kayal et al., 1998) and in humans (Loup et al., 2000). Such changes would be expected to be reflected in altered pharmacology of GABA$_A$R-mediated tonic currents in chronic epilepsy. Although the exact identity of GABA$_A$Rs responsible for the generation of tonic conductances in different cell types is still debated, there is abundant and consistent evidence for the participation of the α5 and δ subunits. Both subunits are present at the extrasynaptic membranes of cortical and hippocampal neurons where they form functional α5β2/3γ2 and α4β2/3δ receptors. While δ-containing GABA$_A$Rs are exclusively extrasynaptic or perisynaptic (Wei et al., 2003), α5-containing receptors can also be found at post-synaptic sites (Serwanski et al., 2006).

The role of these subunits in generating tonic currents has been demonstrated using knockout mice, the α5 inverse agonist L-655,708 and δ subunit preferring agonists THIP and neurosteroids (Stell et al., 2003; Caraiscos et al., 2004). In the hippocampus of control animals α5- and δ-containing GABA$_A$Rs seem to be the main contributors to tonic conductances in vitro. Indeed, double knockout mice lacking both subunits display virtually no tonic GABA$_A$R-mediated currents in CA1 and CA3 pyramidal cells, dentate granule cells and molecular layer interneurons (Glykys et al., 2008). The relative contribution of different GABA$_A$R subtypes to the generation of tonic currents in the hippocampus varies depending on the cell type. In pyramidal cells, α5-containing receptors contribute to ~50% of the tonic conductance, whilst in dentate granule cells, the majority of the tonic current (~70%) is mediated by δ-containing receptors (Glykys et al., 2008). Data from genetically modified mice, however, should be interpreted with caution, as there may be compensatory changes in the expression of other GABA$_A$R subunits. This is illustrated by the observation that, although tonic currents in molecular layer interneurons are almost completely abolished in double knockout mice, neither α5, nor δ deficient animals display attenuated tonic currents in these cells, suggesting up-regulation of the remaining subunit(s). In

addition to the 'conventional' αβγ and αβδ GABA$_A$Rs, a small proportion (~10%) of extrasynaptic receptors on hippocampal pyramidal neurons lacks both γ and δ subunits. These Zn^{2+}-sensitive αβ receptors may also contribute to tonic conductances in hippocampal neurons (Mortensen and Smart, 2006).

GABA$_A$Rs involved in tonic inhibition display much higher affinity towards GABA than those that mediate phasic currents, and thus can detect low levels of the neurotransmitter in the extracellular space (Stell and Mody, 2002; Yeung et al., 2003). The affinity varies substantially depending on the subunit composition of the receptor (Böhme et al., 2004). Therefore, the identity of GABA$_A$Rs expressed by a neuron will define how sensitive it is to ambient GABA, which may fluctuate *in vivo* depending on physiopathological and behavioural state (Bianchi et al., 2003; Vanini et al., 2011). However, increases in the concentration of extracellular GABA will recruit different receptor subtypes (those with lower affinities), so that the relative contribution of different pools of receptors can change. This fact also confounds direct comparisons between the results obtained in different laboratories, when different recording conditions with variable amounts of GABA and/or inhibitors of GABA transport are added to the perfusion solution to facilitate the measurement of tonic currents.

What happens to α5- and δ-containing GABA$_A$Rs in chronic epilepsy? Contrary to expectations, and despite preservation of tonic GABA$_A$R-mediated currents in chronic epilepsy, the overall expression of both subunits is down-regulated (although this varies in different cell types). δ subunit expression in dentate granule cells is reduced following status epilepticus in animal models (Schwarzer et al., 1997; Tsunashima et al., 1997; Peng et al., 2004; Rajasekaran et al., 2010), but see (Brooks-Kayal et al., 1998; Goodkin et al., 2008). The loss of the δ-containing GABA$_A$Rs is apparently accompanied by the up-regulation of α4 subunit expression, leading to increased perisynaptic expression of α4β2/3γ2 receptors (Zhang et al., 2007). Substituting δ subunits with γ2 in an expression system renders α4-containing receptors less sensitive to GABA [there is a 5 fold increase in the EC$_{50}$ for GABA (Brown et al., 2002)]. Therefore, these epilepsy-induced changes in extrasynaptic GABA$_A$R composition can provide a mechanism that allows dentate granule cells to maintain tonic currents provided extracellular GABA concentrations are greater (Zhang et al., 2007). However, it is less certain whether up-regulation of GABA$_A$Rs with lower affinity would explain substantially increased tonic currents observed without supplemented GABA in a similar model (Zhan and Nadler, 2009).

It has also been suggested that the contribution of α5-containing GABA$_A$Rs to tonic currents in dentate granule cells is increased following status epilepticus (Zhan and Nadler, 2009). Indeed, a slight increase of α5 mRNA level has been reported in these neurons (Fritschy et al., 1999; Houser and Esclapez, 2003). Nonetheless, it is unlikely that such a change can fully compensate for the loss of the δ subunits and would be sufficient to augment tonic inhibition as reported in electrophysiological studies.

Down-regulation of δ subunit has an important consequence for drug development strategies. The δ subunit confers sensitivity of GABA$_A$Rs to neurosteroids and hypnotic drug THIP (Gaboxadol), which act as agonists of such receptors potentiating tonic conductances (Belelli and Lambert, 2005; Herd et al., 2007). Supporting decreased expression of δ subunit-containing GABA$_A$Rs, tonic currents in dentate granule cells become insensitive to these drugs following induction of status epilepticus (Zhang et al., 2007; Zhan and Nadler, 2009; Rajasekaran et al., 2010). It is worth noting that other epileptogenic insults (e.g., traumatic brain injury) are not associated with δ subunit down-regulation, and sensitivity of tonic currents in dentate granule cells to δ subunit-targeting drugs is maintained (Pavlov et al., 2011a). Dentate granule cells in tissue resected from humans with intractable temporal lobe epilepsy also

displayed augmented tonic currents upon application of the neuroactive steroid THDOC (Scimemi et al., 2006), suggesting that the pharmacology of tonic currents may vary considerably depending on the aetiology of the disease.

High levels of α5 subunit expression in CA1–CA3 pyramidal cells, normally observed in control animals, are substantially reduced in CA1/CA2 and, to a lesser extent, CA3 regions of epileptic animals (Schwarzer et al., 1997; Tsunashima et al., 1997; Houser and Esclapez, 2003). Although these changes may simply reflect cell degeneration, the absence of a L-655,708-sensitive component of tonic current in surviving pyramidal cells after status epilepticus strongly supports the loss of α5-containing GABA$_A$Rs in these neurons. As this is not compensated by the recruitment of additional δ subunit-containing receptors (Scimemi et al., 2005), it remains to be determined which receptor subtype(s) substitute for the loss of α5-containing receptors in epilepsy.

4. Extracellular GABA levels

A possible explanation for the maintained/increased tonic GABA$_A$R-mediated currents in epileptic tissue is an increase in the concentration of extracellular GABA. In the face of reduced phasic inhibition in epilepsy, it is unlikely that such an increase is due to enhanced synaptic release. Instead, GABA transporters (GATs), the activity of which determines extracellular GABA concentration, can be relatively easily reversed under physiological and pathological conditions (Wu et al., 2003, 2007). There are two main cortical GABA transporters, GAT1 and GAT3: the former is predominantly neuronal and is located at presynaptic GABAergic terminals, while the latter is primarily expressed in glial processes often further away from synapses (Borden, 1996; Ribak et al., 1996; Minelli et al., 1996; Conti et al., 2004). Inhibition or genetic ablation of transporters reduces GABA clearance from the extracellular space and increases tonic GABA$_A$R-mediated currents (Semyanov et al., 2003; Jensen et al., 2003; Keros and Hablitz, 2005). However, the relative role of GAT1 and GAT3 in setting the baseline level of GABA may differ between brain structures. For example, microdialysis data indicate that inhibition of GAT3 does not affect hippocampal GABA concentrations when GAT1 transport is intact (Dalby, 2000), whilst in the thalamus blockade of GAT3 significantly increases tonic conductances indicating a rise in ambient GABA (Cope et al., 2009).

Although there have been reports of compromised expression of GABA transporters during epileptogenesis (Patrylo et al., 2001), other studies have found unaltered function of GAT1 in chronically epileptic animals (Stief et al., 2005). Data from human studies also demonstrate that GABA transport is largely preserved in epilepsy (Mathern et al., 1999; Lee et al., 2006). GATs are electrogenic and GABA transport depends upon voltage and ionic gradients. However, there is no evidence to suggest that GAT1-mediated transport is operating in the reverse mode in epilepsy, as its inhibition substantially increases tonic currents in neurons from chronically epileptic rats (Frahm et al., 2003; Scimemi et al., 2005). Whether this is also the case for the glial GAT3 transporters, or whether reversal of the transporters occurs during seizure activity is not known.

Reversal of GABA transport in certain subpopulations of neurons or individual cells in epileptic tissue cannot be ruled out. Some interneurons in chronic epilepsy may become metabolically more active, express more GAD and have elevated intracellular GABA concentrations (Esclapez and Houser, 1999). Enhanced expression of GATs and an increase in GABA synthesis have also been demonstrated in dentate granule cells in the kainate model of chronic seizures (Sperk et al., 2003). Intracellular accumulation of GABA will favour reversal of the transporters, but the lack of a direct and accurate measure of intracellular GABA concentrations makes

it difficult to predict whether concentrations reach levels that are sufficient to reverse GABA transport.

It should also be noted that the reversal of GATs is not a prerequisite for GABA accumulation in the extracellular space. Depending on the relationship between the level of GABA release and the capacity of GABA transport a reduction of transporter activity may be sufficient to increase extracellular GABA. Indeed, reduced GAT activity without an identifiable decrease of GAT1/GAT3 protein has been documented to potentiate tonic currents in the cerebellum (Ortinski et al., 2006). It remains to be determined whether similar changes occur in the epileptic hippocampus or cortex.

Another yet unexplored mechanism, which may explain persisting tonic inhibition in epilepsy, is transporter-independent GABA release from glia (Lee et al., 2010). Finally, tonic conductance due to spontaneously opening GABA$_A$Rs (Birnir et al., 2000b, 2000a) cannot be ruled out as a potential means of maintaining tonic conductances in neurons in epilepsy. Although spontaneously opening channels have been implicated in the generation of tonic GABA$_A$R-mediated currents in cultured cells (McCartney et al., 2007), whether they contribute to tonic inhibition in neurons *in situ* has not been addressed.

Irrespective of the sources of GABA, the fact that functional, tonically active GABA$_A$Rs are maintained in epilepsy makes them putative targets for anticonvulsant drugs. Therefore, one treatment approach is to increase extracellular GABA concentration by inhibiting its uptake or decreasing breakdown thereby activating extrasynaptic GABA$_A$Rs and dampening network excitability (Sills, 2003). Unfortunately, strategies that aim to increase the level of GABA in brain tissue have been disappointing clinically. Moreover, using this approach can potentially lead to paradoxical pro-epileptic effects. The reasons for this can be manifold. For example, even in the absence of GAT-mediated GABA release in the interictal period, during seizures the rise in extracellular K$^+$ concentration to 10–15 mM may be sufficient to cause depolarisation-induced reverse of neuronal GABA transport. This can also be facilitated by chronic changes in Cl$^-$ homeostasis in epileptic tissue (Cohen et al., 2002; Palma et al., 2006) and/or gradual build-up of intracellular Cl$^-$ during excessive network activity (Glykys et al., 2009). It is also plausible that increased glutamate uptake by astrocytes in response to massive release of the neurotransmitter during seizure activity may cause intracellular Na$^+$ accumulation (as a result of co-transport), and thus trigger the reversal of co-localised glial GABA transporters (Héja et al., 2009). If such reversal of GABA transport indeed occurs during excessive neuronal firing then GAT inhibitors may precipitate or aggravate seizures when network activity reaches a certain level. Compromised GABA transport can therefore have different effects in the interictal and ictal period (Patrylo et al., 2001).

Furthermore, increased extracellular GABA itself may have a pro-convulsive action on the epileptic network. As mentioned earlier, excessive load on the neuronal Cl$^-$ extrusion mechanism together with reduced KCC2 function may push the reversal potential of GABA$_A$Rs to more depolarised values (for review see Blaesse et al., 2009), so that GABA becomes excitatory in some neurons. Although this mechanism has been implicated in epilepsy, the extent of its contribution to ictogenesis remains to be determined.

Another, generally ignored, consequence of increasing GABA concentration is that it can have cell type-specific effect on neuronal excitability. Some interneurons, including certain hippocampal subtypes, have E$_{GABA(A)}$ more positive than their resting membrane potential, and therefore GABA depolarises such cells (Martina et al., 2001; Chavas and Marty, 2003; Vida et al., 2006; Song et al., 2011). A small rise in extracellular GABA concentrations

has an excitatory action on these interneurons, while higher concentrations produce inhibition (Song et al., 2011). Additionally, as mentioned earlier, depending on the subunit composition, the affinity of GABA$_A$Rs expressed in different cells may vary. This would be expected to set a specific range of GABA concentrations that exert an excitatory action for each interneuronal subtype. The firing of interneurons, in which activation of GABA$_A$Rs does not produce depolarisation (Verheugen et al., 1999; Martina et al., 2001), will only be suppressed by elevated GABA. This will disinhibit excitatory neurons counteracting reduction of their excitability. Such changes will be reflected in the balance between excitation and inhibition as extracellular GABA fluctuates. It is apparent that without fully understanding how tonic GABA$_A$R-mediated conductances affect excitability of individual neurons the resulting network effect of manipulating extracellular GABA concentrations in epileptic tissue is hard to predict.

5. GABA$_A$R-mediated tonic currents in shaping neuronal output

Persistent activation of GABA$_A$Rs decreases the membrane input resistance of a neuron and therefore reduces neuronal voltage response to incoming excitation (i.e. decreases amplitude of the excitatory post-synaptic potentials) making it less likely that a neuron fires an action potential. Neurons contribute to information transfer and network function through the generation of action potentials. Each neuron receives excitatory inputs and generates distinct outputs to reflect the input strength. This input–output (I–O) relationship of a neuron reflects the elementary computation performed by the cell (Silver, 2010). The I–O functions are usually presented as either frequency, or probability curves depending on whether the input strength is related to the output frequency, or the probability of action potential generation. The I–O relationship can be modified through a change in gain (slope) or in offset (threshold). These are equivalent to multiplicative/divisive and additive/subtractive operations respectively. An important feature of gain modulation is that it alters the sensitivity of a cell to a given change in input: the steeper the slope of the I–O curve, the lesser change in input is required to generate the same change in the output (Fig. 1A).

Although modelling studies suggest that the presence of a constant conductance would only change the offset of a neuron (Holt and Koch, 1997), a study in cerebellar granule cells has demonstrated that when a neuron is excited by random inputs, shunting inhibition can also modulate the gain of the I–O curve through an impact on input variability (Mitchell and Silver, 2003). Cortical and hippocampal pyramidal cells do not transmit information through continuous high frequency firing, and their I–O relationship are better described by the probability of firing in response to temporally correlated synaptic inputs (Azouz, 2005; Carvalho and Buonomano, 2009). *In vivo* neurons constantly receive thousands of synaptic inputs. The presence of background synaptic activity creates voltage variations at the neuronal membrane and reduces the slope of the I–O function, so that the transfer function of a neuron responds to a wider range of input stimuli (Wolfart et al., 2005). A decrease in membrane input resistance by persistent activation of GABA$_A$Rs would be expected to reduce the magnitude of these variations, and therefore should increase the I–O gain in addition to changing offset. The prediction from this is that increased extracellular GABA concentrations will reduce the excitability of neurons and reduce their dynamic range. Yet, this is not the case. Due to outward rectification tonic GABA$_A$R-mediated conductance in hippocampal CA1 pyramidal neurons has little influence on subthreshold noise, only affecting neurons at spiking threshold. This voltage-dependence of tonic GABA$_A$R-
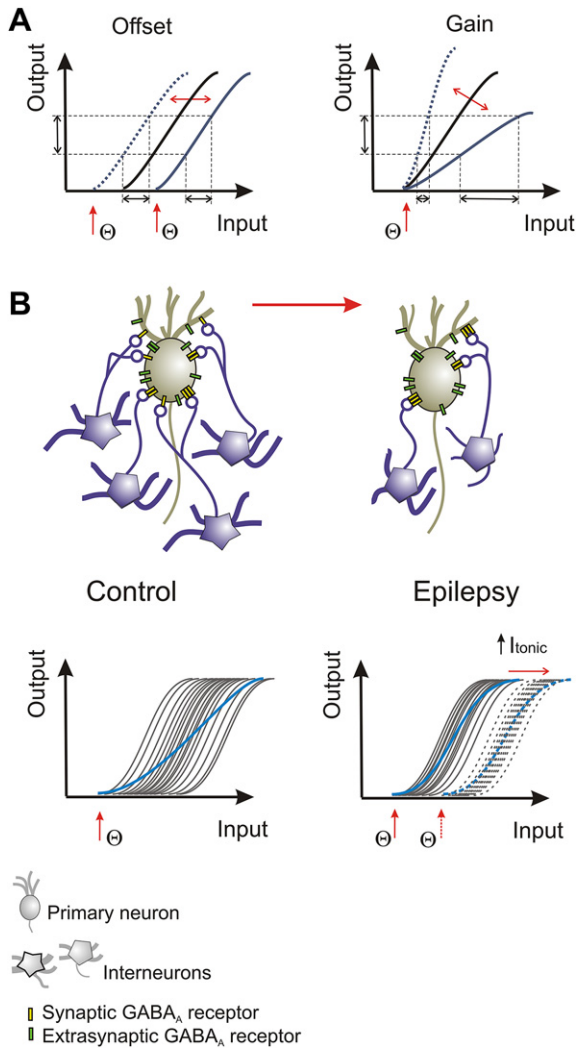
Fig. 1. (A) The input−output function of a neuron (black curve) can be modulated by changing its offset (*left*), or gain (*right*). Offset modulation is associated with changes in the activation threshold (θ), but preservation of neuronal sensitivity to a given change in input. In contrast, gain modulation does not affect the threshold, but alters the sensitivity of a neuron. (B) Epilepsy is associated with the loss of interneurons and decreased synaptic (phasic) inhibition. This may result in narrower dynamic range of individual neurons (grey curves) and population as a whole (blue curves) (see Pouille et al., 2009). Since tonic inhibition is maintained in neurons from epileptic tissue increasing this parameter will reduce excitability of neurons (i.e. shift the threshold; dashed curves on the *right graph*), but will not affect their sensitivity so that the network will remain unstable and prone to sudden changes in excitatory inputs.

mediated currents prevents alterations in the slope of the I−O function as tonic inhibition changes and thus preserves the dynamic range of a neuron (Pavlov et al., 2009).

In contrast to tonic inhibition, changes in phasic inhibition are likely to affect the gain of the I−O relationship (Ferrante et al., 2009; Carvalho and Buonomano, 2009). Moreover, the loss of synaptic contacts in the feed-forward inhibitory circuits in epilepsy not only will affect individual I−O characteristics of neurons, but also may result in a narrower input range, over which the population of cells can respond (Pouille et al., 2009). In this scenario reduced phasic inhibitory synaptic activity will make the neuronal network unstable so that even a small increase in excitation may result in large numbers of neurons firing, promoting seizure generation. Increasing tonic inhibition in CA1 pyramidal neurons may efficiently increase the threshold of network activation by offsetting

neuronal I−O functions, but since tonic inhibition in these cells does not affect neuronal gain, it will not prevent the transition into a hyper-active state once the threshold is reached (Fig. 1B).

6. Concluding remarks

Modulation of GABAergic function remains one of the main strategies in epilepsy treatment. Preservation of tonic GABA$_A$R-mediated conductances in various animal models of epilepsy and in neurons from epileptic human tissue suggests that targeting this form of inhibition can be used to suppress network excitability and prevent seizure generation. However, the successful use of this approach requires a better understanding of epilepsy-induced changes in the pharmacology of tonic currents in cell types that comprise the networks involved in the generation of pathological activity. This knowledge will enable the development of pharmacological tools that will selectively increase tonic inhibition of excitatory cells rather than interneurons. It would be a step forward from the currently used approach in which extracellular GABA concentration is increased globally and, therefore, non-specifically affects all neurons.

Another factor that limits our ability to control network behaviour in epilepsy is the lack of information on how tonic GABA$_A$R-mediated conductances alter action potential output in different neuronal populations. This is further complicated by the fact that GABA's action in certain neurons may switch from hyperpolarising to depolarising (Kaila et al., 1997), facilitated by epilepsy-induced changes in Cl$^-$ transport mechanism and HCN down-regulation (Cohen et al., 2002; Shah et al., 2004; Jung et al., 2007; Wierschke et al., 2010; Pavlov et al., 2011b). The computational consequence of such a switch for tonic GABA$_A$R-mediated signalling, and ultimately neuronal circuit function, has yet to be determined.

Acknowledgements

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