GABA-A Receptor Function in Typical Absence Seizures

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Both human and experimental evidence strongly supports the view of brain region-specific changes in phasic and tonic $GABA_A$ inhibition in typical absence seizures. In neocortex, a decrease in phasic $GABA_A$ inhibition characterizes this non-convulsive epileptic phenotype, though more studies are needed to disclose any neuronal type- and layer-specific alterations. The enhanced tonic $GABA_A$ inhibition, that is present in thalamocortical neurons of genetic and pharmacological models, is both necessary and sufficient for absence seizure generation, and in genetic models it results from a malfunction in the astrocytic GABA transporter GAT-1. Phasic $GABA_A$ inhibition is either unchanged or increased in thalamocortical neurons of absence models. Contradictory results from inbred and transgenic animals still do not allow us to draw firm conclusions on changes in phasic $GABA_A$ inhibition in the GABAergic neurons of the nucleus reticularis thalami. Thus, the long-standing view of a widespread GABAergic loss-of-function in typical absence seizures and childhood absence epilepsy is no longer tenable and model systems that use an indiscriminate block of $GABA_A$ receptors are of no value for understanding the cellular and network mechanisms operating in thalamocortical circuits during typical absence seizures.

A typical absence is a non-convulsive epileptic seizure that is characterized by a sudden and relatively brief impairment of consciousness, occurring concomitantly with a generalized, bilaterally synchronous 'spike (or polyspike) and slow wave discharge' (SWD) at 2.5–4 Hz in the EEG.[1,2] Typical absence seizures are part of the multi-faceted clinical and EEG presentation of many idiopathic generalized epilepsies (IGEs), but in childhood absence epilepsy (CAE) these seizures are the only neurological symptom and are not accompanied by either metabolic, neuropathological or other neurological deficits.[1,2] The human studies reviewed in this chapter, therefore, will be those that relate to CAE, since this is the only IGE where a putative causal link can be made between a typical absence seizure and the underlying genetic variants or pathophysiological mechanisms without the confounding effects of other epileptic and non-epileptic neurological phenotypes.

Typical absence seizures are genetically determined, and the classical 2.5–4 Hz SWD trait has been shown to be inherited in an autosomal dominant manner.[1,2] Indeed, there is strong consensus in describing the occurrence of (typical) absence seizures as a familial disease with a complex multi-factorial genetic background. There is

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also a general consensus, based on some old invasive studies and modern non-invasive imaging investigations, that typical absence seizures originate from abnormal electrical activities in reciprocally connected thalamic and cortical territories - i.e. in what is generally referred to as thalamo-cortical networks, with little or no involvement of other brain areas, including hippocampus, cerebellum and limbic regions.[3-7] Key cellular elements of thalamo-cortical networks include pyramidal cells and interneurons of different cortical layers, the thalamocortical (TC) neurons of sensory thalamic nuclei and their main inhibitory input, i.e. the GABAergic neurons of the nucleus reticularis thalami (NRT). Importantly, the notion that a typical absence seizure is 'generalized' from the very start of the SWD has been recently challenged by the observation that the onset of an absence seizure in humans is associated with paroxysmal activation of discrete, often frontal and parietal cortical regions, spreading then to other cortical regions and to the thalamus.[3,5] The presence of a putative cortical 'initiation site' had previously been shown in genetic rat models of typical absence seizures where, differently from human absences, it is localized in the perioral region of the primary somatosensory cortex.[8,9] Indeed, direct application of the anti-absence drug ethosuximide at this putative 'initiation site', but not 1 mm away from it, readily abolishes absence seizures in freely moving rats.[10]

It is now well established that $GABA_A$ receptor- ($GABA_A$R)-mediated inhibition consists of a phasic component (i.e. the 'classical' IPSPs), that is generated by GABA interacting with synaptic $GABA_A$Rs, and a tonic component (i.e. a persistent membrane hyperpolarization with increased conductance) that is due to GABA activation of perisynaptic or extrasynaptic $GABA_A$Rs.[11] Abnormalities both in synaptic and extrasynaptic $GABA_A$Rs have undoubtedly been of primary significance among the various human molecular genetic alterations[12-15] that have in recent years provided support for the idea that IGEs, and in particular absence seizures, are channelopathies.[16] In this chapter, we first summarize recent evidence demonstrating that enhanced tonic $GABA_A$ inhibition is a common feature of both pharmacological and genetic models of absence epilepsy. In particular, enhanced tonic $GABA_A$ inhibition in TC neurons is both necessary and sufficient for the expression of typical absence seizures, and in genetic models it is not due to a neuronal abnormality but to a malfunction of the astrocytic GABA transporter GAT-1. The available data on phasic $GABA_A$ inhibition, on the other hand, suggest that the changes in this type of GABAergic function observed in animals and humans affected by typical absence seizures are both brain region- and neuronal type-specific. We will then discuss how all these findings on phasic and tonic $GABA_A$ inhibition fit within our current understanding of the pathophysiological mechanisms of typical absence seizures, and propose that the currently prevailing view of an overall GABAergic loss-of-function in typical absence seizures and CAE is no longer tenable.

TONIC $GABA_A$ INHIBITION

Enhanced Tonic $GABA_A$ Inhibition In Genetic Models Of Typical Absence Seizures

The tonic $GABA_A$ current measured *in vitro* in TC neurons of the somatosensory ventrobasal thalamus of different genetic models of absence seizures is enhanced compared to the current in their respective control animals.[17] This is true for a polygenic rat model, i.e., the Genetic Absence Epilepsy Rat from Strasbourg (GAERS)[18] (Figure 1A1–2) and for various mice models with known spontaneous monogenic mutations, including stargazer and lethargic mice[19] (Figure A3). In particular, there is a clear developmental profile of this increased GABAergic function since in GAERS up to postnatal day 16 the current is similar to that in the non-epileptic control (NEC) strain but almost doubles in amplitude at postnatal day 17 (Figure 1A2), and remains elevated well past the time of seizure onset[17] (around postnatal day 30 in this strain[18]). In contrast, no tonic $GABA_A$ current is detected in the GABAergic NRT neurons of GAERS and their respective non-epileptic control strain (unpublished observation), as it is indeed the case in normal Wistar rats.[20]
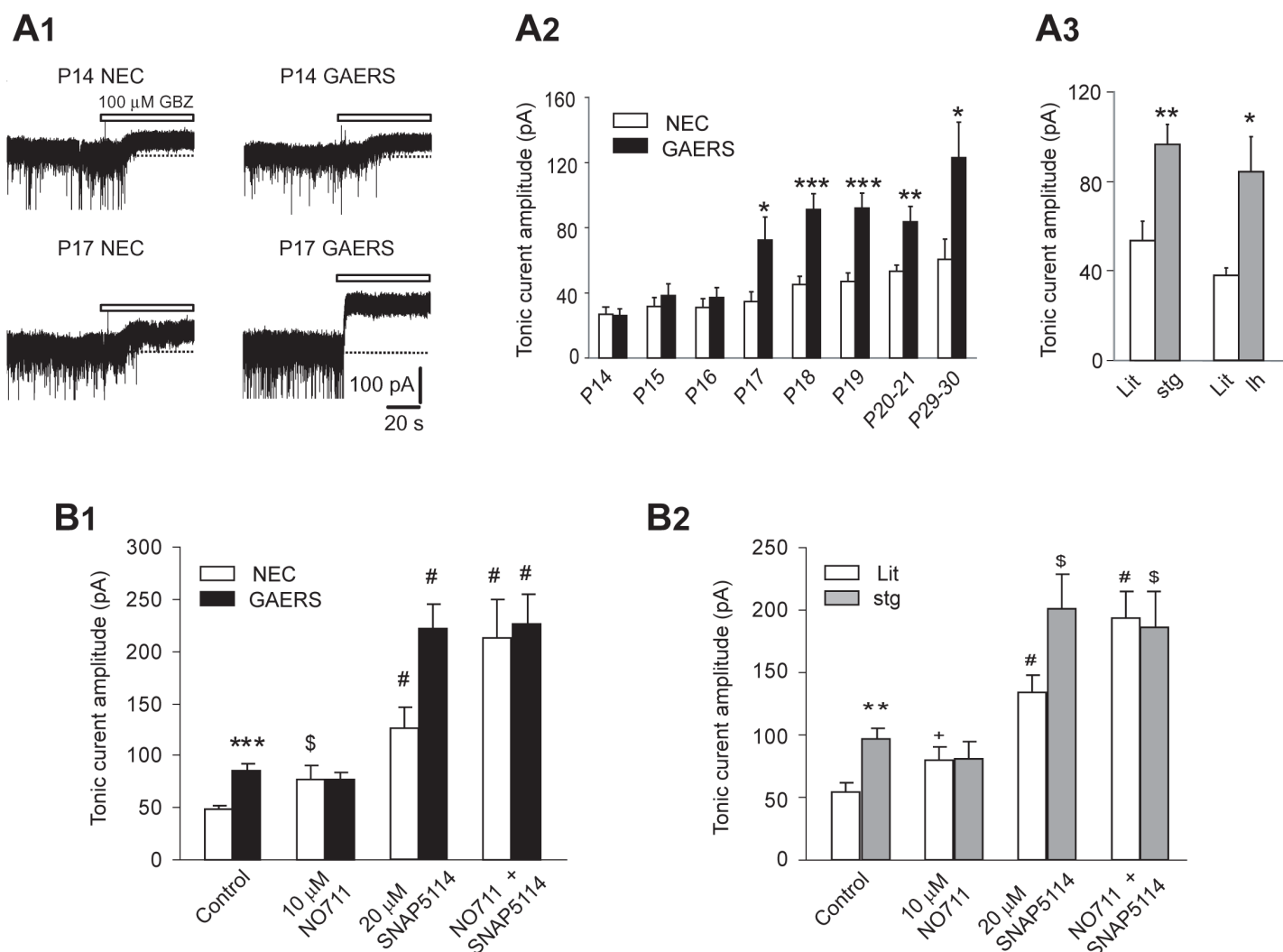
Figure 1. The enhanced tonic $GABA_A$ current in TC neurons of rat and mouse genetic models of typical absence seizures results from a malfunction in the GABA transporter GAT-1. **A1**. Current traces from TC neurons of postnatal day (P) 14 and 17 non-epileptic control (NEC) and GAERS rats indicate the presence of a tonic $GABA_A$ current which is revealed as a shift in baseline current following the focal application of 100 μM gabazine (GBZ, white bars). The amplitude of the tonic current is about two-fold larger in GAERS compared to NEC at P17. **A2**. Tonic current in NEC and GAERS at the indicated postnatal days. **A3**. Tonic $GABA_A$ current in stargazer (stg) (P19-21) and lethargic (lh) (P27-30) mice and respective control age-matched littermates (Lit). **B**. Comparison in P18-21 NEC and GAERS (1), and in P19-21 stargazer (stg) mice and littermates (Lit) (2) of the effects of blocking GAT-1 alone (by 10 μM NO711), GAT-3 alone (by 20 μM SNAP5114), and GAT-1 and GAT-3 together (NO + SNAP) on tonic $GABA_A$ current amplitude of TC neurons. **A2** and **A3**: * $p<0.05$, ** $p<0.01$ and *** $p<0.001$, mutant *vs.* non-mutant animals. **B1** and **B2**: * $p<0.05$, ** $p<0.01$ and *** $p<0.001$, mutant *vs.* non-mutant animals under control conditions; + $p<0.05$, \$ $p<0.01$ and # $p<0.001$, drug *vs.* non-drug for each strain. (A-D: reproduced with permission from Cope et al., 2009, ©Nature Publishing Group).

GAT-1 Malfunction Underlies Increased Tonic $GABA_A$ Inhibition

The enhanced tonic $GABA_A$ current of TC neurons in genetic absence models is not due to increased vesicular GABA release, overexpression of extrasynaptic $GABA_A$Rs, or mis-expression of synaptic $GABA_A$Rs, but results from a malfunction of the GABA transporter GAT-1,[17] despite it being far less abundant in the thalamus than GAT-3.[21] As shown in Figure 1B1-2 in fact, i) block of GAT-1 (by the selective blocker NO711) in GAERS and stargazer has no effect on tonic current amplitude of TC neurons, ii) block of GAT-1 in the respective non-epileptic rats and mice increases tonic current amplitude to similar values to those seen in GAERS and stargazer mice, and iii) the compensatory increase in uptake by GAT-1 that is seen following block of GAT-3 (by the

selective blocker SNAP5114) in non-epileptic animals is lost in both GAERS and stargazer mice.[17] A malfunction in GAT-1 also underlies the increased tonic $GABA_A$ current in TC neurons of lethargic mice.[17] These data support and enlarge previous observations that had shown a reduced GABA uptake by GAT-1[22] and an increased level of extracellular GABA[23] in the ventrobasal thalamus of GAERS compared to NEC. Differently from GAERS and stargazer mice, however, GABA transport by GAT-1 is reversed in lethargic mice, with this transporter being a source of ambient GABA. Interestingly, NO711 increases tonic $GABA_A$ current by a similar amount in dentate gyrus granule cells of GAERS and NEC,[17] indicating that GAT-1 activity is not compromised in a brain area that does not participate in the generation of typical absence seizures[18] and where the distribution of this transporter is primarily neuronal.[24] Indeed, the tonic current of dentate gyrus granule cells is not different between GAERS and NEC.[17]

In summary, therefore, genetic models of typical absence seizures (i.e., GAERS, stargazer, and lethargic mice) show a brain region-specific enhancement of tonic $GABA_A$ current, which in TC neurons is due to increased extracellular GABA level resulting from a malfunction in GABA uptake by astrocytic GAT-1.

Enhanced Tonic $GABA_A$ Inhibition In The GHB Model: Role of $GABA_B$Rs

Systemic (or intrathalamic) injection of γ-hydroxybutyric acid (GHB) is undoubtedly the best-established pharmacological model of typical absence seizures,[25,26] and systemic administration of 4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol) (THIP), a selective agonist at δ subunit-containing extrasynaptic $GABA_A$Rs,[27] has been shown to elicit SWDs in normal animals.[28] Therefore, whereas it is not surprising that THIP dose-dependently enhances the tonic $GABA_A$ current in TC neurons of normal Wistar rats,[17] one would not expect GHB, which does not bind to $GABA_A$Rs and is believed to elicit absence seizures by activation of $GABA_B$Rs,[26] to have an effect on the tonic $GABA_A$ current. However, GHB dose-dependently enhances the tonic $GABA_A$ current in TC neurons of normal Wistar rats[17] (Figure 2A,B) at concentrations that are similar to the brain concentrations that elicit absence seizures *in vivo*.[29] This effect of GHB is not due to some aspecific action since it is abolished by the $GABA_B$R antagonist CGP55845 (Figure 2B). Interestingly, application of CGP55845 alone significantly reduces the tonic $GABA_A$ current amplitude in TC neurons of Wistar rats to 74% of control[17] (Figure 2B), indicating that facilitation of extrasynaptic $GABA_A$Rs by $GABA_B$Rs contributes approximately one quarter of the tonic $GABA_A$ current in normal rats. Importantly, CGP55845 also reduces the tonic current in GAERS, stargazer and lethargic mice to about 55, 65 and 57%, respectively[17] (Figure 2C), suggesting that facilitation of extrasynaptic $GABA_A$R function by $GABA_B$R activation contributes up to half of the tonic current in these genetic models.

In summary, therefore, a GAT-1 malfunction in thalamic astrocytes of mouse and rat genetic models leads to an increase in ambient GABA in the sensory thalamus, which in turn elicits an enhancement in tonic $GABA_A$ inhibition through both direct activation of extrasynaptic $GABA_A$Rs and indirect facilitation of extrasynaptic $GABA_A$Rs via activation of $GABA_B$Rs.

Enhanced Tonic $GABA_A$ Inhibition Of TC Neurons Is Necessary And Sufficient For Typical Absence Seizure Generation

Assessing the impact of enhanced tonic $GABA_A$ current of TC neurons on the expression of absence seizures requires experiments in freely moving animals, where both the behavioural and EEG components of the seizures can be studied without bias introduced by the concomitant use of anaesthetics and/or analgesics. In fact, unrestrained and undrugged GAT-1 KO mice, which have an enhanced tonic $GABA_A$ current in TC neurons, express ethosuximide-sensitive typical absence seizures[17] (Figure 3A,F). Similarly, direct injection of the selective GAT-1 blocker NO711 into the ventrobasal thalamus by reverse microdialysis in normal Wistar rats triggers ethosuximide-sensitive typical absence seizures[17] (Figure 3D,F). Moreover, in δ $GABA_A$R KO mice, which exhibit a markedly reduced $GABA_A$ inhibition in TC neurons, systemic administration of GHB fails to induce absence seizures[17] (Figure 3F). Similarly, the intrathalamic injection of a δ subunit-specific antisense
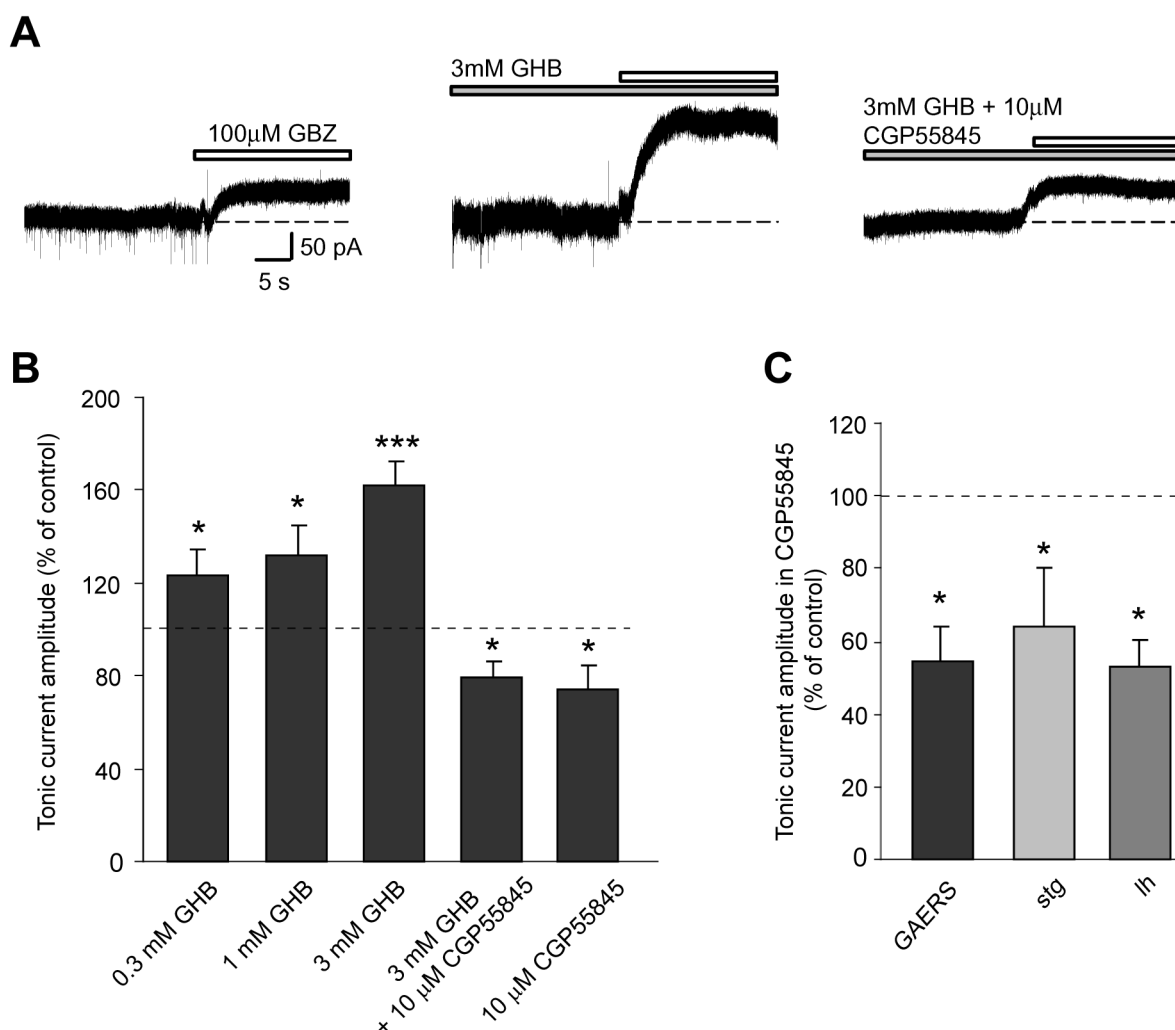
Figure 2. GABA_BRs involvement in the tonic GABA_A current of TC neurons in genetic and pharmacological models of typical absence seizures. A. Current traces form TC neurons of normal Wistar rat showing the GHB-elicited increase in tonic GABA_A current and its block by the GABA_B antagonists CGP55845 (10 μM). **B**. Comparison of the effects of different concentrations of GHB on tonic GABA_A current amplitude in normal Wistar rats, and its block by CGP55845 (10 μM). Note how CGP55845 alone decreases tonic current amplitude compared to control conditions. Values are normalised to the average tonic current in the absence of GHB or CGP55845. **C**. Effect of bath application of 10 μM CGP55845 on tonic GABA_A current in GAERS, stargazer (stg) and lethargic (lh) mice. Values are normalised to the average tonic current amplitude in the absence of CGP55845. **B** and **C**: * $p<0.05$, ** $p<0.01$ and *** $p<0.001$. (A-C: reproduced with permission from Cope et al., 2009, ©Nature Publishing Group).

oligodeoxynucleotide in GAERS strongly decreases both the tonic GABA_A current and spontaneous seizures 1–2 days after injection, whereas a missense oligodeoxynucleotide has no effect[17] (Figure 3E). Finally, intrathalamic administration of the δ subunit-specific agonist THIP in normal Wistar rats elicits absence seizures in a concentration-dependent manner, an effect that is reversed by systemic administration of ethosuximide[17] (Figure 3C,F). Taken together, these data show that enhanced tonic GABA_A inhibition in TC neurons is both necessary and sufficient for the generation of typical absence seizures. In addition, they provide a mechanistic explanation for the aggravation of absence seizures that is observed in humans and experimental models following systemic and intrathalamic administration of drugs that increase GABA levels, including tiagabine, a GABA uptake blocker, and vigabatrine, a GABA transaminase blocker.[18,30–32]
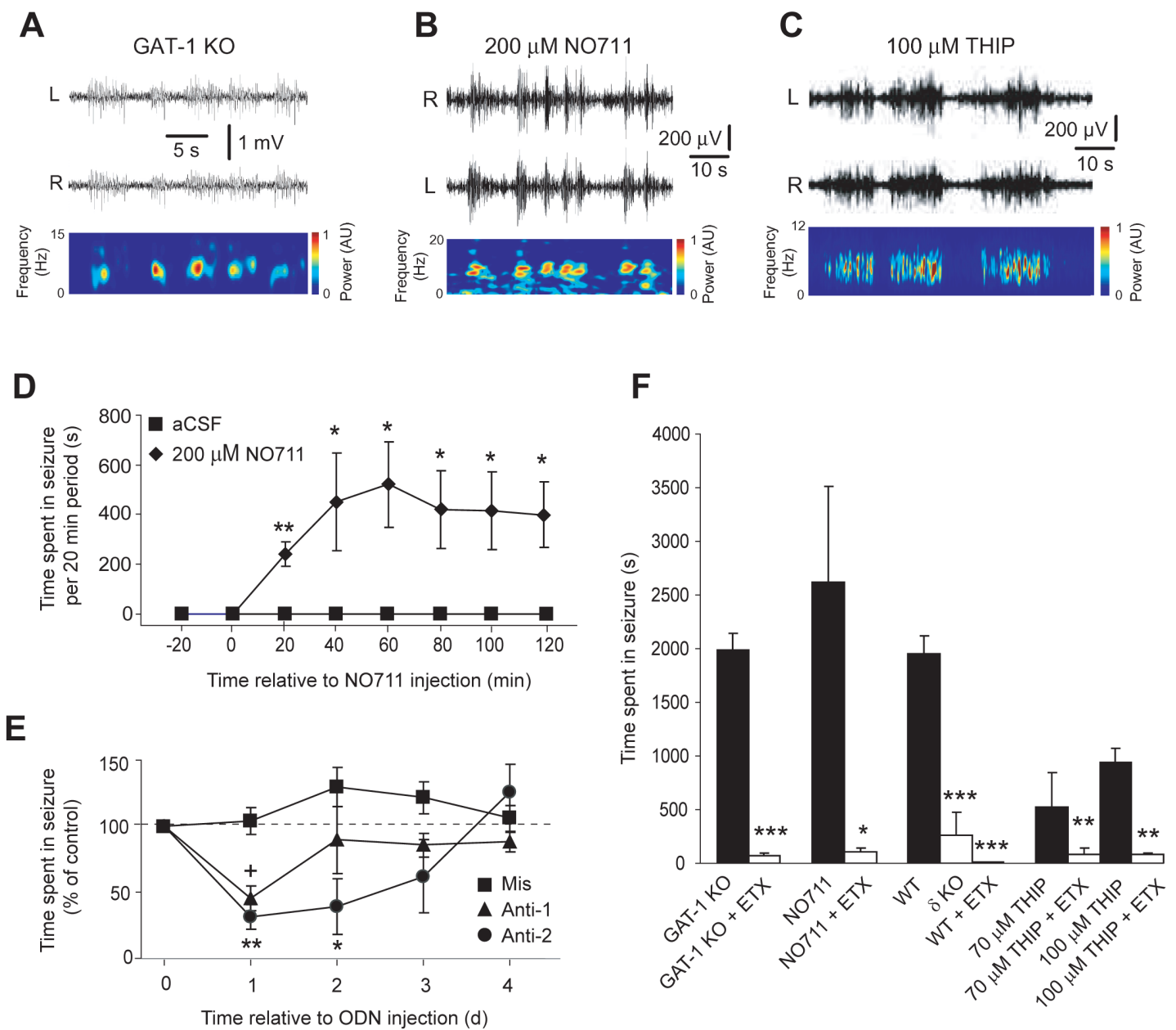
Figure 3. The tonic GABA$_A$ inhibition in TC neurons is both necessary and sufficient for typical absence seizure generation. A. Bilateral (L = left, R = right hemispheres) EEG traces from a freely moving GAT-1 knockout (KO) mouse showing spontaneous SWDs (spectrogram of the R trace is illustrated below). **B**. Bilateral EEG traces from a normal Wistar rat following intra-thalamic administration by reverse microdialysis of 200μM of the selective GAT-1 blocker NO711 (spectrogram of the L trace is illustrated below). **C**. Bilateral EEG traces from a normal Wistar rat following intra-thalamic administration by reverse microdialysis of 100μM THIP (spectrogram of the R trace is illustrated below). **D**. Time-course of the induction of SWDs by intra-thalamic administration of NO711. **E**. SWDs are substantially reduced in GAERS 1 and 2 days following a single intrathalamic injection of a small and large dose of a δ-subunit antisense oligodeoxynucleotide (Anti-1 and Anti-2, respectively), but not of a missense oligo (Mis). **F**. Summary histograms showing the cumulative (over 1–2 hours) time spent in seizures for different transgenic and pharmacological mice and rat models, and the abolition of their SWDs by systemic administration of ethosuximide (100 or 200 mg/kg/ip). * p<0.05, ** p<0.01 and ***p<0.001. (A-F: reproduced with permission from Cope et al., 2009, © Nature Publishing Group).

Significance Of Tonic GABA$_A$ Inhibition In Typical Absence Epilepsy

The discovery of an increased tonic GABA$_A$ current in TC neurons represents the first abnormality that i) is common to both well-established pharmacological and genetic models of typical absence seizures, irrespective of

species and known up-stream mutations, ii) is manifested both before and after the developmental onset of seizures, iii) contributes to the exquisite sensitivity of experimental absence seizures to selective GABA$_B$R agonists and antagonists, and iv) explains the aggravating effects of GABAergic drugs in both human and experimental absence seizures. Importantly, these results, together with the presence of powerful GABA$_A$ IPSPs in the majority of TC neurons during absence seizures *in vivo*[33,34] (Figure 4A1–2) (see below), lead to another significant conclusion, i.e., that studies aiming at reproducing typical absence seizures by indiscriminatly blocking GABA$_A$Rs of TC neurons35–38 are inherently flawed.

The finding that the increased tonic GABA$_A$ inhibition in TC neurons of genetic models is due to a malfunction of GAT-1 shifts the emphasis from a neuronal to an astrocytic aetiology of absence epilepsy. The impaired GAT-1 activity in GAERS is not caused by a decreased expression of GAT-1 mRNA or protein levels in either thalamus or cortex.[17] Also, GAT-1 cDNA from GAERS, stargazer and lethargic mice presents no genetic variants, whereas the mutations responsible for absence seizures in stargazer and lethargic mice are not present in GAERS.[17] Potential abnormalities that may lead to a reduced GAT-1 function, but have not yet been tested, include the inability of this protein to reach the outer astrocytic membrane, an alteration in its subcellular location and/or abnormalities in its phosphorylation. Similalry, we are aware of no study that has investigated GAT-1 (or GAT-3) genetic variants in human CAE.

Experimental typical absence seizures can be elicited or aggravated by selective GABA$_B$R agonists and can be blocked by selective GABA$_B$R antagonists, applied either systemically or intrathalamically.[39–41] Because about 50% of the tonic GABA$_A$ current observed in TC neurons of GAERS, stargazer and lethargic mice is abolished by a GABA$_B$R antagonist17 (Figure 2C), the behavioural and EEG effects of GABA$_B$R-selective drugs on typical absence seizures can no longer be simply explained by the ability of these drugs to affect GABA$_B$-mediated IPSPs and/or presynaptic GABA$_B$Rs, but should also take into account the positive modulation by GABA$_B$Rs of the tonic GABA$_A$ inhibition in TC neurons.

PHASIC GABA$_A$ INHIBITION

The picture concerning phasic GABA$_A$ inhibition in typical absence seizures is much more complex than that of tonic GABA$_A$ inhibition, since contradictory results have emerged from studies in various experimental models. For sake of clarity, therefore, the analysis of available evidence on phasic GABA$_A$ inhibition will be presented separately for each main neuronal type of the thalamo-cortical network, i.e. cortical neurons, TC neurons and the GABAergic neurons of the NRT.

Phasic GABA$_A$ Inhibition In Cortex

Among the various mutations in GABA$_A$R subunits, those that have been identified in related or unrelated CAE patients are: α1(S326fs328X), β3(P11S), 3(S15F), β3(G32R), γ2(R43Q), γ2(R139G) and γ2(IVS6+2T•G).[12–15,42] Functional analysis of these mutant proteins expressed in heterologous systems has shown that all of them bring about a marked decrease in GABA responses.[12] Importantly, humans carrying the γ2(R43Q) mutation have been shown to have a decreased short-interval intracortical inhibition assessed with transcranial magnetic stimulation, leading to cortical facilitation.[43] γ2(R43Q) mutant mice constructed by homologous recombination express spontaneous ethosuximide-sensitive absence seizures.[44] Moreover, despite the fact that the γ2 subunit has an almost ubiquitous expression and is apparently required for functional synaptic GABA$_A$Rs, these mice exhibit a brain region-specific alteration in phasic GABA$_A$ inhibition, since cortical layer 2/3 pyramidal cells but not TC or NRT neurons show a reduction in miniature IPSCs (mIPSCs) compared to age-matched wildtype littermates.[44] Whether the region-specificity of this malfunction is also present in humans with the γ2(R43Q) mutation, or only occurs in mice because of some species-specific promoters or silencers, is not known at present. Nevertheless, together with showing the physiological effect of a human genetic variant in a "true" physiological system as opposed to hetereologous expression systems, the key significance of this finding is that

A1

EEG

IPSPs

Intra - TC

20 mV

500 ms

A2

EEG

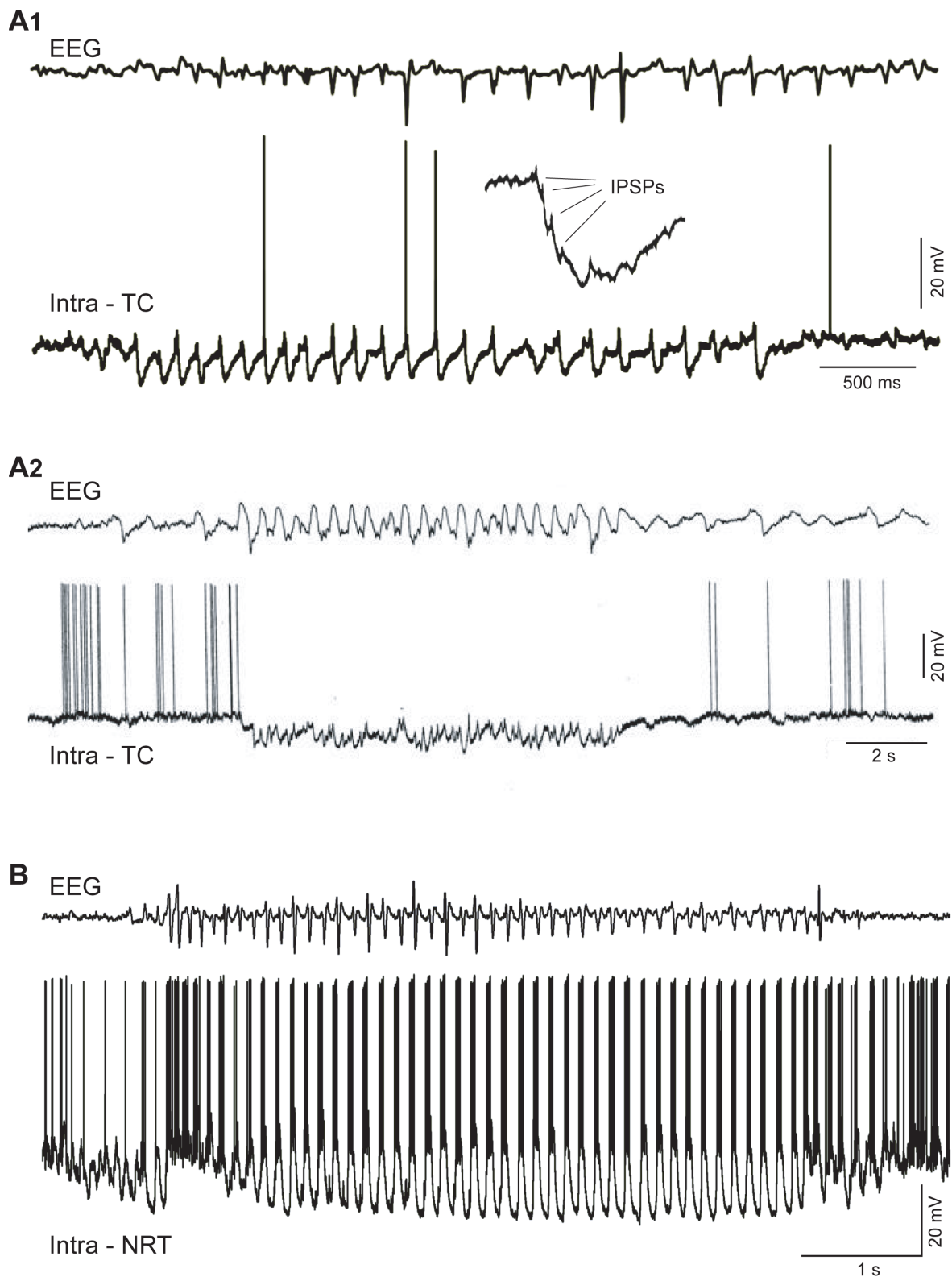20 mV

Intra - TC

2 s

B

EEG

Intra - NRT

20 mV

1 s

Figure 4. Intracellular correlates of TC and NRT neuron activity during spontaneous SWDs *in vivo*. A1. Intracellular recording (bottom trace) from a TC neurons in GAERS *in vivo* during a spontaneous SWD (top trace) shows the presence of bursts of IPSPs occurring in synchrony with each spike and wave complex. Note the individual IPSPs (arrows) in the enlarged burst in the inset. **B**. Intracellular recording (bottom trace) from a cat TC neurons *in vivo* during a SWDs (top trace) shows the presence of IPSPs superimposed on a long-lasting hyperpolarization that lasts for the entire duration of the SWD. **B**. Intracellular recording (bottom trace) from an NRT neurons in GAERS *in vivo* during a spontaneous SWD (top trace) shows the presence of large low-threshold Ca^{2+} potential in synchrony with each spike and wave complex. (A1 and B: reproduced with permission from Crunelli and Leresche 2001, © Nature Publishing Group; A2: reproduced with permission from Steriade and Contreras 1995, © Society for Neuroscience).

it is the first clear evidence that the downstream abnormalities of a human genetic variant in CAE can be inhibition that brain region-specific. Importantly, the cortex-specific abnormality in phasic $GABA_A$ results from the human γ2(R43Q) mutation exquisitely complements previous experimental data showing that 1) in felines *in vivo* the localized block of $GABA_A$Rs by cortical application of inhibition in the thalamus, does elicit SWDs,[33] and bicuculline, which leaves intact phasic $GABA_A$ inhibition in TC neurons is either unaffected or 2) in rat and mouse genetic models phasic $GABA_A$ increased compared to their respective non-epileptic controls[17,44–47] (see below).

On the basis of indirect evidence, a decreased cortical GABAergic inhibition has also been suggested to occur in layer 2/3 regular spiking neurons[48] as well as in layer 5 pyramidal neurons[49] of adult Wistar Albino Glaxo/Rij (WAG) rats, another well established polygenic model of typical absence seizures.[50] However, no change is observed in mIPSCs in pyramidal cell and interneurons of cortical layers 2–3 of young, pre-seizure GAERS,[45] and cortical GABAergic inhibition is intact in the feline generalized penicillin epilepsy model.[51]

In summary, the evidence from a human mutation indicates that a decreased phasic $GABA_A$ inhibition in cortex characterizes typical absence seizures, though further studies are needed to clarify the extent of this decrease both in terms of different cortical regions, layers and neuronal types: this additional work might shed light on the existing discrepancies on changes in phasic $GABA_A$ inhibition among experimental models.

Phasic GABA$_A$ Inhibition In TC Neurons

A reduced or absent phasic $GABA_A$R function in the thalamus also characterizes the current view of the pathophysiology of typical absence seizures. While this may be partly true for the intra-NRT inhibition it certainly does not hold for TC neurons. Thus, both in felines that show spontaneous or cortical bicuculline-induced SWDs[33] as well as in the well-established GAERS model[34] the vast majority (60 and 94%, respectively) of TC neurons recorded *in vivo* during SWDs exhibit bursts of $GABA_A$ IPSPs, each tightly synchronized with the EEG spike and wave complex (Figure 4A1–2). Indeed, the rise time, amplitude, frequency and decay time constant of mIPSCs and spontaneous IPSCs (sIPSCs) measured in TC neurons *in vitro* are not different between GAERS and NEC both prior to,[45] and after spontaneous seizure manifestation[17] (i.e. postnatal days 12–25, and postnatal day 30, respectively), and paired pulse depression of evoked IPSCs is similar between the two strains[45] (Figure 5B3). As mentioned earlier, no change in TC neuron IPSCs occurs in mice carrying the human γ2(R43Q) mutation,[44] and no change in IPSC properties has been detected in TC neurons of β3 KO mice[52] which show absence seizures as part of a much more complex neurological phenotype. Also, in lethargic, stargazer and tottering mice sIPSCs in TC neurons are similar to those in their respective littermates,[17] and no difference has been found in evoked IPSCs in lethargic and tottering mice compared to control mice.[47] Finally, an increase in mIPSCs frequency, potentially leading to enhanced phasic inhibition, is observed in TC neurons of the absence seizure-prone DAB/2J mouse strain.[46]

In a similar manner to the genetic models, in the best-established pharmacological model of absence seizure, i.e. the GHB model, a net increase in phasic $GABA_A$ inhibition is observed in TC neurons of the ventrobasal thalamus.[53] This is because whereas GHB reversibly and dose-dependently decreases the amplitude of all sensory[54] and corticothalamic EPSCs[53] (Figure 5A1), the two main excitatory drives to TC neurons, at low concentrations (250 μM-1 mM) it only affects the $GABA_A$ IPSCs in some but not all TC neurons[53] (Figure 5A2–3). In particular, 250 μM GHB produces an effect in <10% of tested TC neurons, whereas at 0.5-1 mM it only decreases half of the recorded IPSCs (Figure 5A4–5). Thus, at brain concentrations (250 μM - 1 mM) similar to those that elicit absence seizures *in vivo* GHB brings about not only the previously described GABA$_B$R- and K+-dependent hyperpolarization[26,55] and an increase in tonic $GABA_A$ inhibition[17] (see above) but also an imbalance between the excitatory and inhibitory drive to TC neurons, leading to a net increase in their phasic $GABA_A$ inhibition. This, in turn, will help to impose that periodic phasic inhibition that sculptures the electrical behaviour of TC neurons during SWDs as observed *in vivo* in feline[56] and rat[57] models (Figure 4A1–2).

On the basis of all this evidence from both genetic and pharmacological models, as well as from mice expressing the human γ2(R43Q) mutation, it is therefore surprising that the data in support of the presence of an enhanced or unchanged phasic GABAergic function in TC neurons have been selectively dismissed over the last 15 years, such that textbooks and topical reviews[58–62] still present the pathophysiological mechanisms of TC neuron activity during typical absence seizures as the one that is observed *in vitro* during application of a GABA$_A$R antagonist.[35,36,38] It is also surprising that the *in vivo* evidence which is often used to support this view is the ability of bicuculline (or other GABA$_A$R antagonists) to generate, in ketamine-xylazine anaesthetized rats, strong field potentials at 3 Hz[37], that are claimed to represent SWDs even if their sensitivity to ethosuximide or other anti-absence drugs was not tested. Indeed, it is highly unlikely that these field potentials represent SWDs, since the ketamine-xylazine combination, as other general anaesthetic, are known to abolish the SWDs of any well-established *in vivo* model of absence epilepsy.[18,51,63]

In summary, therefore, the presence of these serious issues of interpretation, together with the evidence showing an increased tonic and an unchanged/increased phasic GABA$_A$ inhibition in TC neurons of genetic and pharmacological models, strongly support the conclusion that the block of thalamic GABA$_A$Rs that continues to be used in many *in vitro* and some *in vivo* studies does at best elict some form of thalamic hyperexcitability of as yet unknown pathophysiological relevance, but definitely not the activity that is present during typical absence seizures.

Phasic GABA$_A$ Inhibition In NRT Neurons

The existance of contradictory data makes it difficult at present to draw a unifying picture of the changes in the phasic GABA$_A$ inhibition of NRT neurons that are associated with an absence seizure phenotype. Starting from inbred genetic models, mIPSCs recorded from NRT neurons of pre-seizure GAERS show a 67% higher frequency, a 25% larger amplitude and a 40% faster decay than those in age-matched NEC.[45] Moreover, paired-pulse depression of evoked GABA$_A$ IPSCs is significantly smaller (46%) in NRT neurons of GAERS than NEC[45] (Figure 5B1–2). This smaller paired-pulse depression of IPSCs in GAERS would undoubtedly ensure a consistent hyperpolarizing drive to help promote the expression of the strong, low threshold Ca^{2+} potential-mediated bursts of action potentials that are the hallmark of NRT neuron firing at each spike and wave complex *in vivo*[56,57] (Figure 4B). Moreover, an increase in mIPSC frequency, potentially leading to enhanced phasic GABA$_A$ inhibition, is observed in NRT neurons of the absence seizure-prone DAB/2J mouse strain.[46] Finally, an almost complete disappearance of the α3 subunit, that in the thalamus is selectively expressed in NRT neurons[64], has been reported in these GABAergic neurons from WAG rats,[65] suggesting a potential loss of function.

Surprisingly, however, α3 KO mice do not show spontaneous absence seizures and indeed exibit a small reduction in GHB-elicited seizures compared to wildtype littermates, a result that has been interpreted as resulting from a powerful compensatory gain in phasic GABA$_A$ inhibition in NRT neurons.[66] On the other hand, since unknown mechanisms lead to this unexpected compensatory increase in NRT GABA$_A$ inhibition following deletion of the α3 subunit, the lack of spontaneous absence seizures and the relative resistance to pharmacologically induced absence seizures may also be due to additional compensatory changes in phasic (or tonic?) GABA$_A$ inhibition in cortex, or tonic inhibition in thalamus, all of which were not investigated in that study.[66] Further evidence for a pro-absence role of a decreased phasic GABA$_A$R function in NRT neurons has also come from the observation of an increase in high frequency discharges at 3 Hz in β3 subunit KO mice, which show a massive reduction in sIPSP frequency and amplitude in NRT, but no change in TC neurons.[52] Since these β3 KO mice exhibit a large variety of neurological deficits and are considered a model of Angelman's syndrome, it is difficult to unequivocally assign a causative role for this decreased intra-NRT inhibition in typical absence seizures.

In summary, whereas in inbred models and models with spontaneous mutations there is either an increase or no change in intra-NRT phasic GABA$_A$ inhibition, data from two transgenic mice suggest that a decrease in this
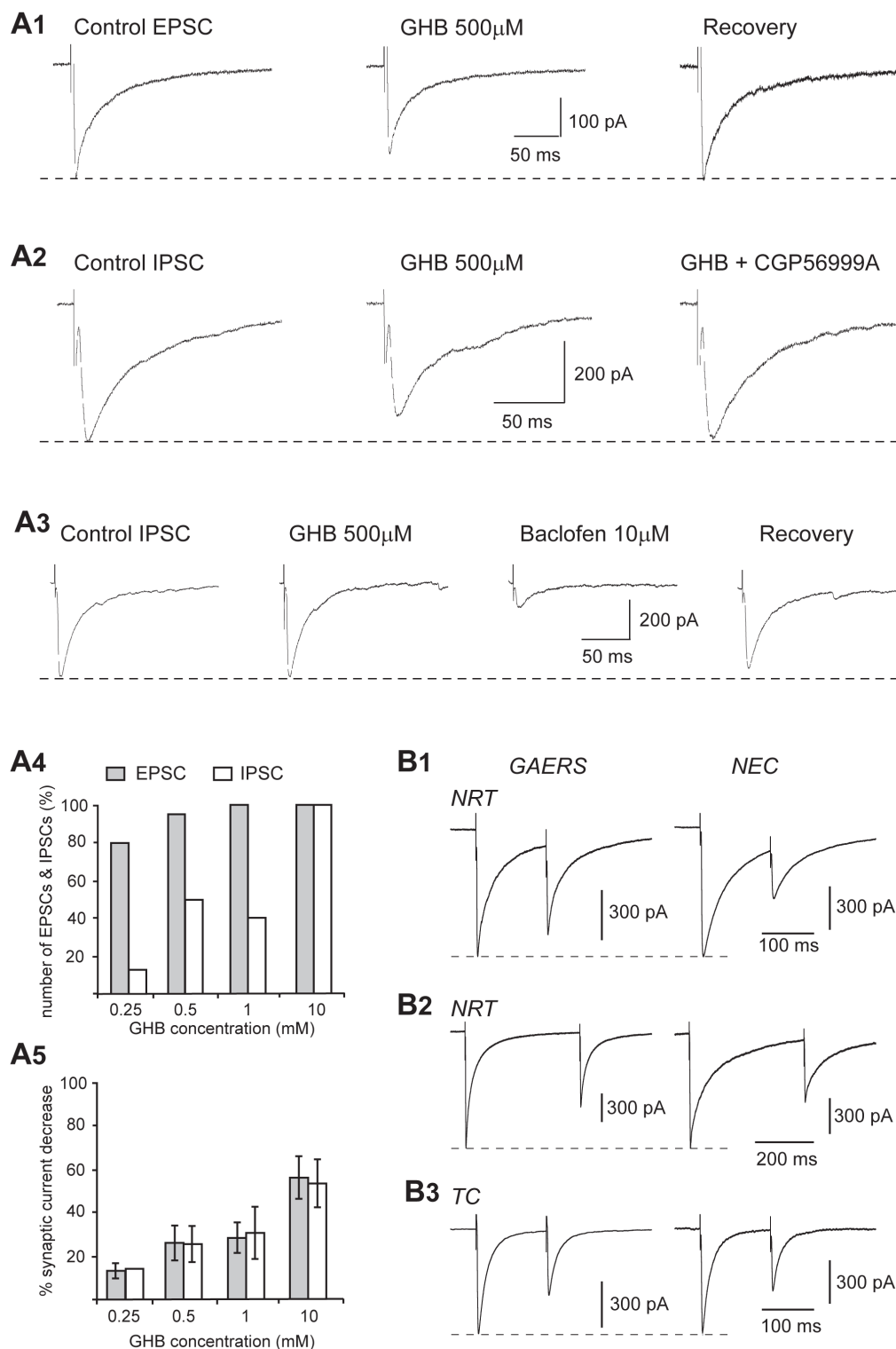
Figure 5. Phasic GABA$_A$ inhibition in TC and NRT neurons of genetic and pharmacological models of typical absence seizures. **A1**. GHB reversibly decreases the amplitude of a cortical EPSC recorded in TC neurons. **A2**. Example of an NRT-derived IPSC (recorded in a TC neuron) that is decreased by GHB. The effect is blocked by the GABA$_B$ antagonist CGP56999A (100 nM). **A3**. Example of an NRT-derived IPSC (recorded in a TC neuron) that is unaffected by GHB (500 μM). Following washout of GHB, the IPSC is reversibly reduced by the selective GABA$_B$ agonist baclofen (10 μM). **A4**. All cortical EPSCs are decreased by GHB, while only a number of NRT-derived IPSCs are sensitive to low concentrations of this drug. **A5**. Plot showing the similar potency of GHB on cortical EPSCs and NRT-derived IPSCs. **B**. Paired-pulse depression of IPSCs in NRT neurons of GAERS is much smaller in NEC than in GAERS for interstimulus interval similar (1) but not longer (2) than that of the SWDs. **B3.** Paired-pulse depression of IPSCs recorded in TC neurons is similar between GAERS and NEC. (A: reproduced with permission from Gervasi et al, 2003, © Society for Neuroscience; B: reproduced with permission from Bessaih et al., 2006, © American Physiological Society).

NRT synaptic function has a pro-absence effect. Thus, it may be tempting to conclude that abnormalities in intra-NRT phasic $GABA_A$ inhibition are not a necessary condition for the expression of typical absence seizures, a view supported by the lack of changes in NRT IPSCs of mice carrying the human γ 2(R43Q) mutation[44]. In this respect, it is worth noting that the anti-absence effect of clonazepam in humans and experimental models[67,68] may not be solely due to its ability to increase phasic $GABA_A$ inhibition in NRT,[69] since α3 subunit-containing $GABA_A$Rs that are the target of this benzodiazepine are also present in neocortical neurons.[70]

ROLE FOR PHASIC AND TONIC GABA$_A$ INHIBITION IN THE GENESIS OF ABSENCE SEIZURES

The evidence reviewed in this chaper suggests the following scenario concerning the cellular contribution of phasic and tonic $GABA_A$ inhibition to typical absence seizures. A decreased phasic $GABA_A$ inhibition in the neocortex leads or contributes to a paroxysmal development of normal 5–9 Hz oscillations in a discrete somatosensory cortical "initiation site". This strong and highly synchronous cortical output powerfully excites the GABAergic neurons of the NRT, which respond by generating low-threshold Ca^{2+} potential-mediated bursts of action potentials at every spike and wave complex of the SWD. This rhythmic burst firing, in turn, results in bursts of IPSPs in TC neurons which override cortical excitation. Concomitantly, ambient GABA levels around TC neurons abnormally increase due to reduced GABA uptake by GAT-1, enhancing extrasynaptic $GABA_A$R function directly, and indirectly by a $GABA_B$R-dependent facilitation. Enhanced tonic inhibition persistently hyperpolarises the TC neurons and increases their membrane conductance, reducing their action potential output, with low threshold Ca^{2+} potential-mediated bursts of action potentials rarely occurring. Furthermore, the responsiveness of TC neurons to excitatory, sensory synaptic inputs is reduced, 'gating' information flow through the thalamus, abolishing responsiveness to external stimuli and causing behavioural arrest. Importantly, the rhythmic IPSP bursts entrain TC neuron output to each cycle of a SWD, providing a sparse but synchronised input to the cortex and maintaining paroxysmal activity in thalamo-cortical networks.

CONCLUDING REMARKS

Despite the long-standing notion of an overall decrease in $GABA_A$R function in typical absence seizures, a critical appraisal of the human and experimental evidence strongly supports the view of different, brain region-specific changes of both phasic and tonic $GABA_A$R-mediated inhibition in this non-convulsive epileptic phenotype. In particular, a decreased phasic $GABA_A$ inhibition characterizes cortical activity, though more studies are needed to disclose any neuronal type- and layer-specific abnormalities. An enhanced tonic inhibition, which results from a malfunction of the astrocytic GAT-1 transporters, together with an unchanged or increased phasic inhibition is present in TC neurons of both genetic and pharmacological models of typical absence seizures. Contradictory results in different species and transgenic animals and the reliance on unsuitable *in vitro* model systems still do not allow a clear view of the changes in phasic $GABA_A$ inhibition that accompany typical absence seizure in NRT neurons. Thus, thalamic and cortical model systems where $GABA_A$Rs are indiscriminately blocked do not reproduce the complex pattern of alterations in these neurotransmitter receptors that are observed in human and experimental absence seizures, and are therefore of no value for understanding the cellular mechanisms operating in thalamo-cortical networks during typical absence seizures.

Acknowledgments

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