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Neurosteroids and epilepsy

Giuseppe Biagini[a], **Gabriella Panuccio**[b], and **Massimo Avoli**[b,c]

[a]Dipartimento di Scienze Biomediche, Università di Modena and Reggio Emilia, Modena, Italy

[b]Montreal Neurological Institute and Departments of Neurology and Neurosurgery and of Physiology, McGill University, Montréal, Québec, Canada

[c]Dipartimento di Medicina Sperimentale, Prima Facoltà di Medicina e Chirurgia, Sapienza Università di Roma, Rome, Italy

Abstract

Purpose of review—Neurosteroids are a family of compounds synthesized directly in the brain by transforming cholesterol into pregnenolone, which is then converted to compounds such as allopregnanolone and allotetrahydrodeoxycorticosterone. In view of their ability to modulate neurotransmission, neurosteroids may influence the clinical course of epileptic disorders. In this review, we highlight two emerging properties of neurosteroids, that is, their anticonvulsant and antiepileptogenic activities.

Recent findings—It has been shown that fluctuations in neurosteroid synthesis, such as those seen in response to stress or during the ovarian cycle, determine an increase in seizure threshold. Moreover, increased neurosteroid synthesis, presumably occurring in glial cells during epileptogenesis, delays the appearance of recurrent spontaneous seizures in an animal model of temporal lobe epilepsy; such an effect may be due to augmented tonic γ-aminobutyric acid type A receptor-mediated inhibition. Finally, clinical trials with ganaxolone, an allopregnanolone analogue, have demonstrated beneficial effects in pharmacoresistant epileptic patients, whereas finasteride – which interferes with neurosteroid synthesis – facilitates seizures in catamenial epilepsy.

Summary—The overall evidence suggests that neurosteroids may represent a novel therapeutic strategy in epileptic disorders and a future perspective to control epileptogenicity.

Keywords

epilepsy; epileptogenesis; γ-aminobutyric acid type A receptor; glia; neurosteroids

Introduction

Neurosteroids are currently under clinical evaluation for their potential therapeutic use in epileptic disorders. Clinical trials have demonstrated anticonvulsant effects for ganaxolone, an analogue of the neurosteroid allopregnanolone, in pharmacoresistant epileptic patients

Correspondence to Massimo Avoli, MD, PhD, McGill University, Montreal Neurological Institute, 3801 University, room 794, Montreal, QC H3A 2B4, Canada Tel: +1 514 998 6790; massimo.avoli@mcgill.ca.

[1]. Moreover, Herzog and Frye [2] have reported of a patient affected by catamenial epilepsy, whose seizures were controlled by progesterone administration, but were exacerbated by treatment with finasteride, an inhibitor of allopregnanolone and allotetrahydrodeoxycorticosterone (THDOC) synthesis [3]. The anticonvulsant effect of progesterone is mediated by its nongenomic actions (i.e. independent of progesterone receptor expression), as administration of progesterone maintains powerful antiseizure effects in progesterone receptor-knockout mice [4]. The mechanism underlying these clinical effects is presumably based on the ability of allopregnanolone (a progesterone metabolite) and THDOC to modulate γ-aminobutyric acid type A ($GABA_A$) receptor-mediated transmission as these molecules can increase both tonic and phasic inhibition [5]. The $GABA_A$ receptor-related anticonvulsant effects of neurosteroids are further supported by experimental evidence obtained from animal models [5–8]. Furthermore, recent findings have substantiated the role of neuroactive steroids in catamenial epilepsy [9•,10•]. Finally, neurosteroids appear to be involved in temporal lobe epilepsy (TLE) as suggested by their ability to delay the establishment of this chronic condition following pilocarpine-induced status epilepticus in rats [11,12]. Here, we will address these aspects by reviewing recently available information on both clinical and experimental findings and by presenting unpublished data obtained in our laboratories.

Neurosteroids as modulators of neuronal excitability

Neurosteroids are synthesized after the conversion of cholesterol to pregnenolone by the cytochrome P450 cholesterol side chain cleavage (P450scc) enzyme [3]. Pregnenolone is then turned into 17α-hydroxypregnenolone or into progesterone, which are precursors of a cascade of diverse steroid derivatives that are in turn able to interact with various neurotransmitters. Neurosteroids are in fact capable of interacting with $GABA_A$, *N*-methyl-D-aspartate (NMDA), glycine, and opioid σ_1 receptors (reviewed by [13]).

Two classes of neurosteroids can be distinguished, depending on their metabolism by addition of sulfate residues, conferring these compounds different modulatory properties on neuronal excitability. Whereas substances belonging to the family of nonsulfated neurosteroids, such as allopregnanolone and THDOC, enhance $GABA_A$ receptor function (as described in the next paragraph, but see also [14•]), sulfated neurosteroids present with more complex properties. Overall, this class of neurosteroids appears to increase neuronal excitability, acting as negative $GABA_A$ receptor modulators and/or by enhancing glutamatergic activity. However, several investigations have provided evidence for a negative modulatory effect of sulfated neurosteroids on glutamate-mediated neurotransmission. Glutamate receptor subunit composition appears to be a key factor influencing the modulatory effect of neurosteroids [15] and further investigation is needed to address the pathophysiological relevance of such variable effects in the context of epileptic disorders. These puzzling observations have been recently reviewed [16,17•].

Given the well known role of GABAergic inhibition in epileptic disorders, the remaining review will focus on the effects induced by neurosteroids on $GABA_A$ receptor function. The interaction of nonsulfated neurosteroids with $GABA_A$ receptors exhibits concentration-dependent mechanisms of action [5]: in the nanomolar range (e.g. during stress and oestrus),

they act as modulators of $GABA_A$ receptors, whereas at micromolar concentrations (as those physiologically observed during parturition), they can directly open $GABA_A$ channels. It has been suggested that neuroactive steroids may potentiate $GABA_A$ currents via interaction with the α1 subunit, whereas direct activation of the $GABA_A$ receptor relies upon the interaction with both α1 and β2 subunits [18].

As shown in Fig. 1, $GABA_A$ receptor activation can generate two types of current, depending on their location and subunit composition: synaptic receptors give rise to phasic 'transient' currents in response to GABA release from synaptic vesicles, whereas extrasynaptic and perisynaptic receptors respond to low levels of ambient GABA by generating a tonic 'always on' current [19]. The tonic GABAergic current is largely contributed by α5 and δ-subunit-containing $GABA_A$ receptors [20]. Interestingly, mice lacking the $GABA_A$ δ-subunit present with an attenuated response to neurosteroids [21], a finding consistent with the view that tonic rather than phasic inhibition may represent the preferential target for neurosteroid modulation (see [22•] for review).

Neurosteroids and epileptic seizures

Catamenial exacerbation of epileptic seizures provides compelling evidence of the involvement of steroids in this chronic neurological disorder, a phenomenon explained by the influence on $GABA_A$ receptor plasticity exerted by fluctuations in steroid production and their conversion in neurosteroids (see for review [23•]). However, the view that neuroactive steroids may exert a protective role against seizures has been recently challenged by the emergence of opposite effects that these compounds exhibit when studying absence seizures. Although progesterone appears to improve catamenial epilepsy [10•], its derivative allopregnanolone promotes spike-and-wave discharges in Wistar Albino Glaxo rats of Rijswijk (WAG/Rij), a model of absence seizures [24]. Moreover, a role for allopregnanolone in disinhibiting neuronal networks has recently emerged based on experimental data obtained from seizure-prone rats [25]. The following paragraphs will specifically address the effect of neurosteroids as studied in different epilepsy models and will focus on the possible clinical implications of these findings.

Stress and seizures

Stress is among the most frequent seizure precipitating conditions reported by epileptic patients [26], a phenomenon that may be related to corticosterone secretion [27•]. However, the possibility that stressing stimuli may also exert a protective action against epileptic seizures has emerged over the past decades (see [28•] for extensive review). This effect may rest on the conversion of steroid hormones into neuroactive steroids.

Selye [29,30] was the first to describe the anesthetic and anticonvulsant properties of progesterone, another stress-related steroid. More recently, the anticonvulsant effect associated with stress has been ascribed to the conversion of deoxycorticosterone in neuroactive metabolites such as THDOC [31]. The role of stress in restraining seizure activity has recently been reappraised by Verleye *et al.* [32••] in a mouse model of anxiety. In this study, Balb/cByJ mice exposed to a short immobilization stress exhibited a lower seizure threshold in response to $GABA_A$ receptor blockade when neurosteroid synthesis was

limited by treatment with finasteride. This effect was antagonized by allopregnanolone, whereas progesterone was ineffective, suggesting that only neurosteroids are able to modulate seizures by potentiating $GABA_A$ receptor function at physiological concentrations.

Catamenial epilepsy

Finasteride has been reported to increase seizure activity in a patient affected by catamenial complex partial seizures, which were instead controlled by progesterone [2], suggesting that modulation of neurosteroid pathway can play a role in controlling seizures, at least when hormonal dependence is present. Further support to this view has been recently provided by experimental evidence obtained from a rodent model of catamenial epilepsy, in which progesterone withdrawal or finasteride treatment has been shown to exacerbate pentylenetetrazol-induced and pilocarpine-induced seizures [10•].

The anticonvulsive effect related with physiological fluctuations in neurosteroids during the ovarian cycle has been identified by analyzing the changes in δ-$GABA_A$ receptor subunit in mice in which seizure threshold was assessed by kainic acid treatment [33]. It was found that the tonic $GABA_A$ receptor-mediated current doubled in amplitude during late diestrus in dentate gyrus granule cells. This change was mirrored by a 43% increase in hippocampal δ-$GABA_A$ subunit, and the two findings were related with fluctuations in progesterone plasma levels. Consistent with the findings obtained in the dentate gyrus, mice injected with kainic acid presented with a doubled latency to seizure appearance during diestrus (i.e. when progesterone level peaks) and the average seizure duration was much shorter. All these phenomena were abolished by treating mice with a δ-$GABA_A$ subunit antisense mRNA, which reduced the expression of this $GABA_A$ subunit by 36% and the tonic current by 76%. Thus, when associated with increased neurosteroid availability occurring during the ovarian cycle, variations in δ-$GABA_A$ subunit decrease seizure susceptibility. Overall, these findings point at neurosteroids replacement therapy as a novel therapeutic approach for the treatment of catamenial epilepsy [10•].

Temporal lobe epilepsy

Different isoforms of 5α-reductase and 3α-hydroxysteroid dehydrogenase – which are both involved in the synthesis of allopregnanolone and THDOC – have been identified in the hippocampus and cerebral cortex of patients affected by refractory TLE [34]. The mRNA levels for these enzymes were similar to those found in brain tumor specimens obtained from nonepileptic individuals. However, the mRNA for 3α-hydroxysteroid dehydrogenase isoform 2 was higher in the hippocampus than in the temporal neocortex of TLE patients. Interestingly, allopregnanolone serum levels were found to be significantly decreased in male, but not in female TLE patients compared with healthy controls.

Further support to the view that neurosteroids are involved in TLE comes from evidence obtained from animal models. Studies on pilocarpine-treated mice have shown a 50% decrease in δ-subunit expression of $GABA_A$ receptor in the dentate gyrus molecular layer 30 days after status epilepticus. This change was accompanied by loss of efficacy in reducing granule cells excitability by THDOC [35]. However, experiments on pilocarpine-treated rats have revealed only a transient loss (24–48 h after status epilepticus) of the ability of

allopregnanolone to modulate $GABA_A$ receptor-mediated currents in the dentate gyrus [36]. A more recent study has demonstrated a compensatory increase in $GABA_A$ γ2-subunit, so that tonic inhibition was substantially preserved in the dentate gyrus of epileptic mice [37], though the efficacy of THDOC in modulating of the tonic GABAergic current was decreased. In a different model of status epilepticus induction, obtained by continuous hippocampal electrical stimulation, neurons recorded from epileptic rat brain slices were found to be insensitive to low (10–30 nmol/l) but responsive to high (100 nmol/l) allopregnanolone concentrations [38], thus explaining the inconsistencies found in mice [35,37] and rats [36] treated with pilocarpine.

Overall, these findings suggest that the ability of neurosteroids to potentiate $GABA_A$-mediated currents is lost after status epilepticus in chronic epileptic animals, whereas the site for direct receptor activation is preserved and could enhance GABAergic transmission. It must, however, be emphasized that the implication of experimental data on neurosteroids and TLE for clinical practice remains unclear.

Absence seizures

A more complex role is played by neurosteroids in primary generalized epileptic disorders such as absence seizures. The hallmark of generalized absence epilepsy is the generation of spike-and-wave discharges, which are largely contributed by GABAergic mechanisms involved in thalamocortical interaction [39].

Both allopregnanolone and pregnenolone sulfate [intra-peritoneally (i.p.) injected] promote, in a dose-dependent manner, spike-and-wave discharges in WAG/Rij rats [24]. Consistently, a recent study by Pisu *et al.* [40••] described an increase in allopregnanolone and THDOC along with overexpression of α4 and δ-$GABA_A$ subunits in this rodent model of absence seizures. However, Citraro *et al.* [41] had previously reported in the same model that the effects induced on generalized spike-and-wave activity by local neurosteroid microinjection are both dose-dependent and region-specific. Moreover, these investigators found opposite effects when comparing allopregnanolone with pregnenolone sulfate, which, as summarized above, depend on the resulting interaction with both $GABA_A$ and glutamate receptor function. These findings highlight the variability of neurosteroid action in absence seizures and indicate that caution must be taken when considering neurosteroid treatment for this type of epilepsy.

Neurosteroids and epileptogenesis

The P450scc enzyme is found in neurons, oligodendrocytes and astrocytes [3], and in activated microglial cells [12] (Fig. 2a). Thus, neurosteroid levels in brain tissue that has been hit by status epilepticus could be altered as a consequence of neuronal damage as well as of glial cell activation. To assess how these changes could affect epileptogenesis, we have recently studied P450scc immunoreactivity after pilocarpine-induced status epilepticus in adult rats [11]. We have found a highly significant increase in P450scc both in neurons and glial cells. However, the neuron-specific changes were limited to the first few days after status epilepticus, whereas those in glial cells were long-lasting and approximately equivalent to the latent period preceding the appearance of spontaneous recurrent seizures.

In addition, by varying the duration of the initial status epilepticus induced by pilocarpine, we discovered a clear correlation between the extent of P450scc induction and the duration of the latent period, which was significantly longer in rats exposed to at least 180 min of continuous seizures compared with others exposed to shorter status epilepticus [12] (Fig. 2b). It should also be emphasized that young, 3-week-old rats exposed to short (60 min) status epilepticus present with a more pronounced induction of P450scc than that seen in adult animals (Fig. 2b), and in fact, contrary to adult animals, young rats rarely present with stage V seizures during the chronic epileptic period (Fig. 2c) [42].

The role of neurosteroids in delaying seizure onset in the pilocarpine model has been further tested by treating rats exposed to status epilepticus with finasteride, a procedure that could anticipate the appearance of stage V seizures in rats experiencing at least 180 min of status epilepticus, but not in those experiencing 90 min only [12]. In addition, we compared the effects of finasteride in adult (8-week-old) and young (3-week-old) rats exposed to 60 min of status epilepticus. Again, finasteride was ineffective in altering the latent period in adult rats, in which P450scc is scarcely induced by such a short exposure to status epilepticus (Fig. 2c). On the contrary, seizure manifestation was anticipated in approximately 50% of young rats. Therefore, these findings suggest that neurosteroid synthesis is related to the extent of P450scc induction in glial cells consequent to status epilepticus.

A high neurosteroid synthesis can influence epileptogenesis presumably by providing $GABA_A$ receptor activation, whereas low neurosteroid levels are unable to potentiate $GABA_A$ receptor transmission in epileptic rats [38]. Consistent with this hypothesis, $GABA_A$-mediated inhibition should be enhanced during the period immediately following the induction of prolonged status epilepticus. Remarkably, ongoing investigations in our laboratories suggest that tonic $GABA_A$ current is more pronounced in rat pyramidal-like subicular neurons as early as 3 days following a 2 h long pilocarpine-induced status epilepticus (Fig. 3). These findings may be particularly relevant to better understand the dynamic interplay between epileptogenesis and neurosteroid–GABA interactions and may represent a focal point for future investigation on the mechanisms underlying the antiepileptogenic action of neuroactive steroids.

Conclusion

The involvement of endogenous neurosteroids and their synthetic analogues as modulators of neuronal excitability in the context of epileptic disorders still remains under investigation, due to the variability of their influence on neurotransmission. In fact, the modulatory effect of these neuroactive compounds depends on their class (e.g. sulfated vs. nonsulfated), the neurotransmitter receptor subunit composition, and the pathophysiological mechanisms underlying specific epileptic disorders. The literature summarized here clearly indicates that the ability of neurosteroids to modulate neuronal excitability resides primarily in the enhancement of GABAergic inhibitory tone. This physiological characteristic may, however, yield opposite effects, depending on the contribution of GABAergic mechanisms to epileptiform synchronization that are specific to different epileptic syndromes. In rodent models of TLE, glia-derived neurosteroids have proved to exert antiepileptogenic actions, an intriguing finding that let us foresee the possibility of employing neurosteroids or their

analogues to prevent the development of a chronic epileptic condition in high-risk patients. This is particularly relevant in epileptology, as there are, to date, no pharmacological agents capable of stopping epileptogenesis.

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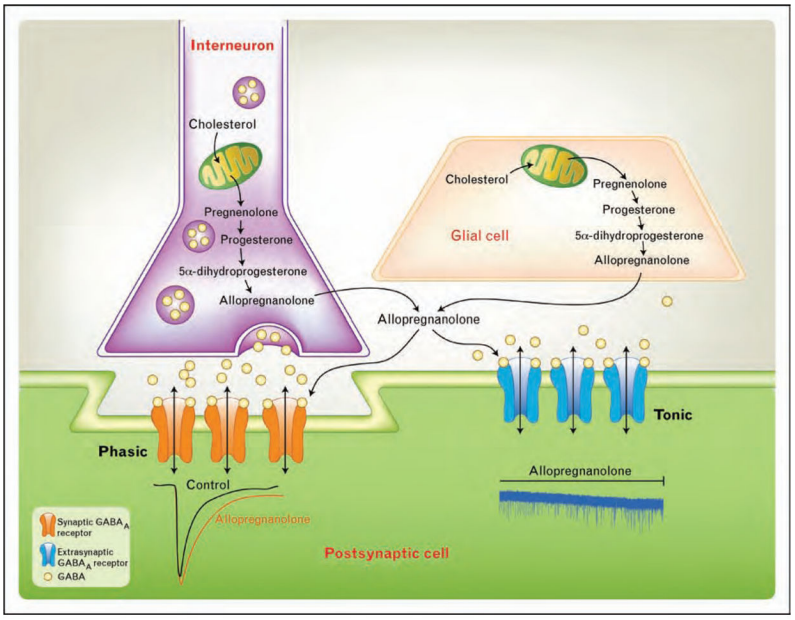

Figure 1.

Neuroactive steroids and their actions on GABAergic inhibition

γ-Aminobutyric acid (GABA) released from an interneuron interacts with $GABA_A$ receptors at synaptic (orange) and extrasynaptic (blue) locations, generating phasic and tonic inhibitory currents, respectively. The schematic drawings below the two receptors illustrate the corresponding effect of allopregnanolone on $GABA_A$-mediated currents, showing an increase in the decay time constant of synaptic events and an increase in the inhibitory tone as revealed by the downward shift in the holding current.

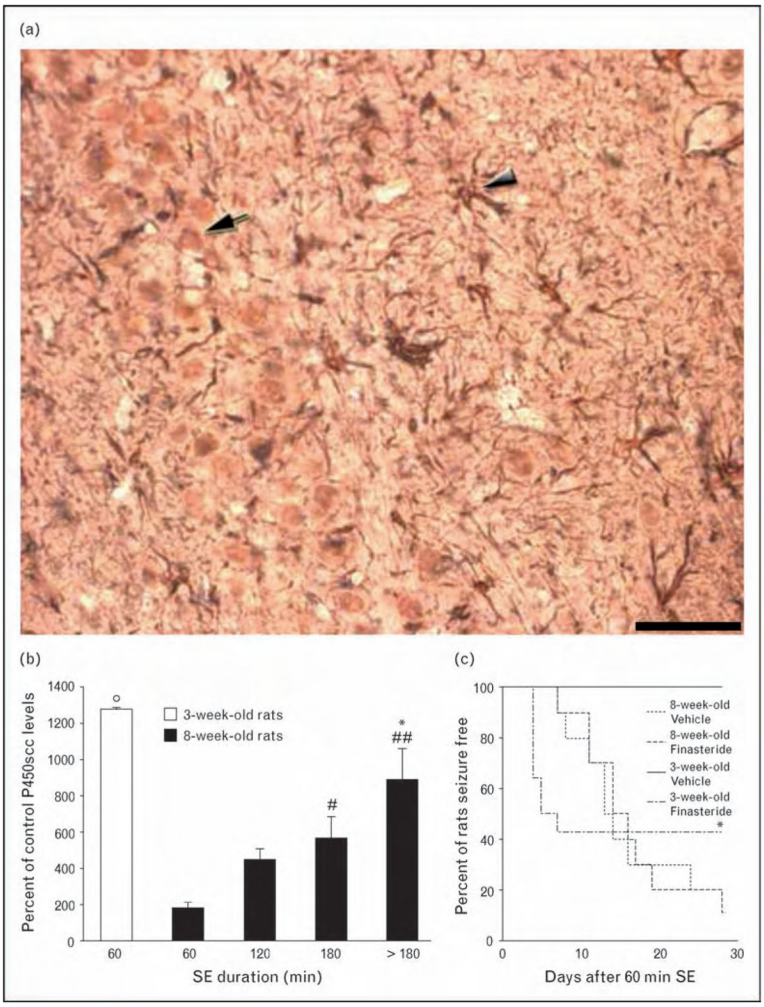

Figure 2.

Induction of neurosteroids after status epilepticus modulates epileptogenesis

(a) Triple immunostaining with antibodies against the neuron-specific nuclear protein (NeuN, arrow), the glial fibrillary acidic protein (GFAP) expressed in astrocytes (arrowhead), and the cholesterol side chain cleavage enzyme associated with the cytochrome P450 (P450scc). Methods were previously detailed (ref. [12]); scale bar is 50 μm. (b) Quantification of P450scc immunoreactivity in astrocytes of the CA3 region in young (3-week-old) and adult (8-week-old) rats exposed to variable duration of status epilepticus, obtained by injecting pilocarpine (ref. [42]). $^{*}P<0.05$ vs. 120 min status epilepticus; $^{\#}P<0.05$, $^{\#\#}P<0.01$ vs. 60 min status epilepticus, adult rats; $^{\circ}P<0.05$ vs. adult rats; one-way analysis of variance (ANOVA) and the Tukey's test. (c) Finasteride (100 mg/kg subcutaneously, injected from the 4th up to the 28th day after status epilepticus induction) significantly ($^{*}P<0.05$ vs. vehicle-treated young rats, log rank test) anticipated the onset of seizure activity in young rats. SE, status epilepticus.

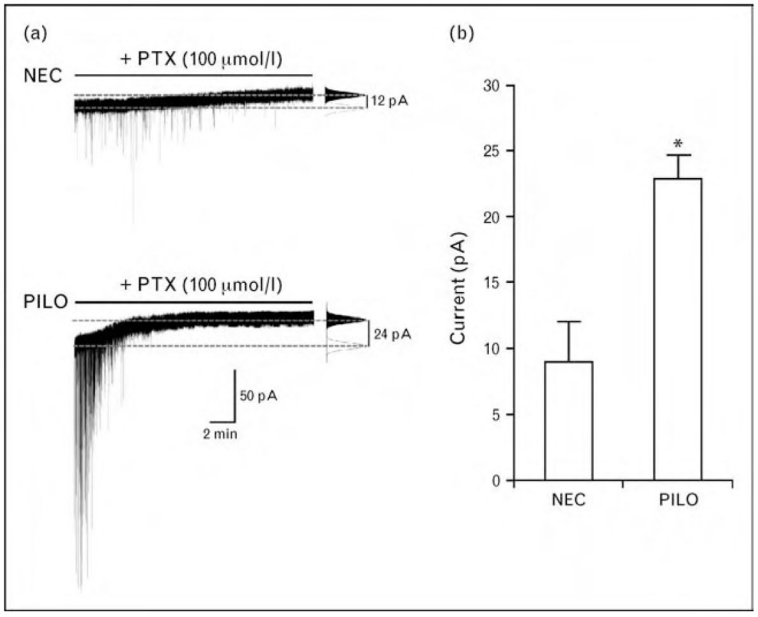

Figure 3.

GABAergic tonic inhibition is enhanced in the rat subiculum after pilocarpine-induced status epilepticus

(a) Patch clamp recordings (Vm = −70 mV) of subicular pyramidal-like neurons obtained from a nonepileptic control (NEC) and a pilocarpine-treated (PILO) rat, 3 days after induction of status epilepticus lasting for 2 h. In symmetric chloride condition, tonic GABAergic activity is revealed by a positive shift in the holding current during application of the $GABA_A$ receptor blocker picrotoxin (PTX, 100 μmol/l). On the right of each trace, all-point histograms indicate the normalized amount of tonic current generated during control condition (white) and after application of PTX (black), as measured at the corresponding dashed gray lines. (b) Pyramidal-like subicular neurons present with enhanced tonic current as early as 3 days after pilocarpine-induced status epilepticus (NEC: 9.06 ± 3.02 pA; pilocarpine: 22.97 ± 1.78 pA; n =7 and 5, respectively; P =0.003, unpaired t-test. Data are expressed as mean ± SEM).