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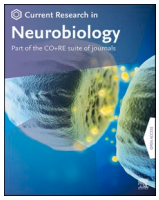

$GABA_B$ receptor outward currents are transiently disclosed by the convulsant 4-aminopyridine *in vitro*

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ABSTRACT

The K^+ channel blocker 4-aminopyridine (4AP) has been extensively used to investigate the mechanisms underlying neuronal network synchronization in both *in vitro* and *in vivo* animal models of focal epilepsy. 4AP-induced effects are paralleled by an increase in both excitatory and inhibitory neurotransmitter release, but the mechanisms of action of 4AP on neuronal networks remain unclear. By employing simultaneous whole-cell patch clamp and field potential recordings from hippocampal CA3/4 pyramidal layer of acute brain slices obtained from mice (n = 30), we found that the appearance of epileptiform discharges induced by 4AP (100 μM) is consistently preceded by the transient recurrence of presumptive $GABA_B$ outward currents, which are not mirrored by any field activity. These $GABA_B$ outward currents still occurred during application of ionotropic glutamatergic antagonists (n = 12 cells) but were blocked by the $GABA_B$ receptor antagonist CGP55845 (n = 7). Our findings show that the transient occurrence of distinct $GABA_B$ outward currents precedes the appearance of 4AP-induced neuronal network synchronization leading to epileptiform activity in the rodent hippocampus *in vitro*.

1. Introduction

4-aminopyridine (4AP) is a K^+ channel blocker (Mitterdorfer and Bean, 2002; Storm, 1990) that has been extensively used over the last four decades to identify the fundamental mechanisms that lead to epileptiform activity in *in vitro* (Perreault and Avoli, 1989, 1991, 1992; Rutecki et al., 1987; Voskuyl and Albus, 1985) and *in vivo* (Fragoso--Veloz et al., 1990; Lévesque et al., 2013; Mihaly et al., 1990) animal models of focal epilepsy. The occurrence of 4AP-induced epileptiform discharges are paralleled by an increased release of both excitatory and inhibitory neurotransmitters (Buckle and Haas, 1982; Perreault and Avoli, 1991, 1989; Rutecki et al., 1987; see for review Avoli et al., 2023) but the exact pharmacological dynamics of these effects remain elusive. Therefore, we employed simultaneous whole-cell patch clamp and field potential recordings from hippocampal CA3/4 region, in acute brain slices obtained from mice, to investigate the progressive changes in neuronal network excitability that occur after bath application of 4AP. We report here that the appearance of synchronous epileptiform events is preceded by the transient occurrence of $GABA_B$ outward currents that are not mirrored by any field activity and spontaneously disappear once epileptiform discharges occur.

2. Materials and methods

Animals - We used male and female mice (P21–P50) of mixed genetic backgrounds (Pv-Cre, n = 21; CaMKII-ChR2, n = 4; CaMKII-Cre, n = 2; wild type, n = 3). All animals were bred and maintained in-house with free access to food and water and 12 h light/dark cycles. All procedures were approved by the McGill University Animal Care Committee and performed according to the protocols and guidelines of the Canadian Council on Animal Care. No significant difference between mice of different genetic background were observed.

Mouse brain slice preparation and maintenance – Mice were deeply anesthetized with isoflurane and were transcardially perfused with carbogenated (95% O_2 and 5% CO_2) ice-cold (~4 °C) choline chloride cutting solution containing 132.5 mM of choline chloride, 2.5

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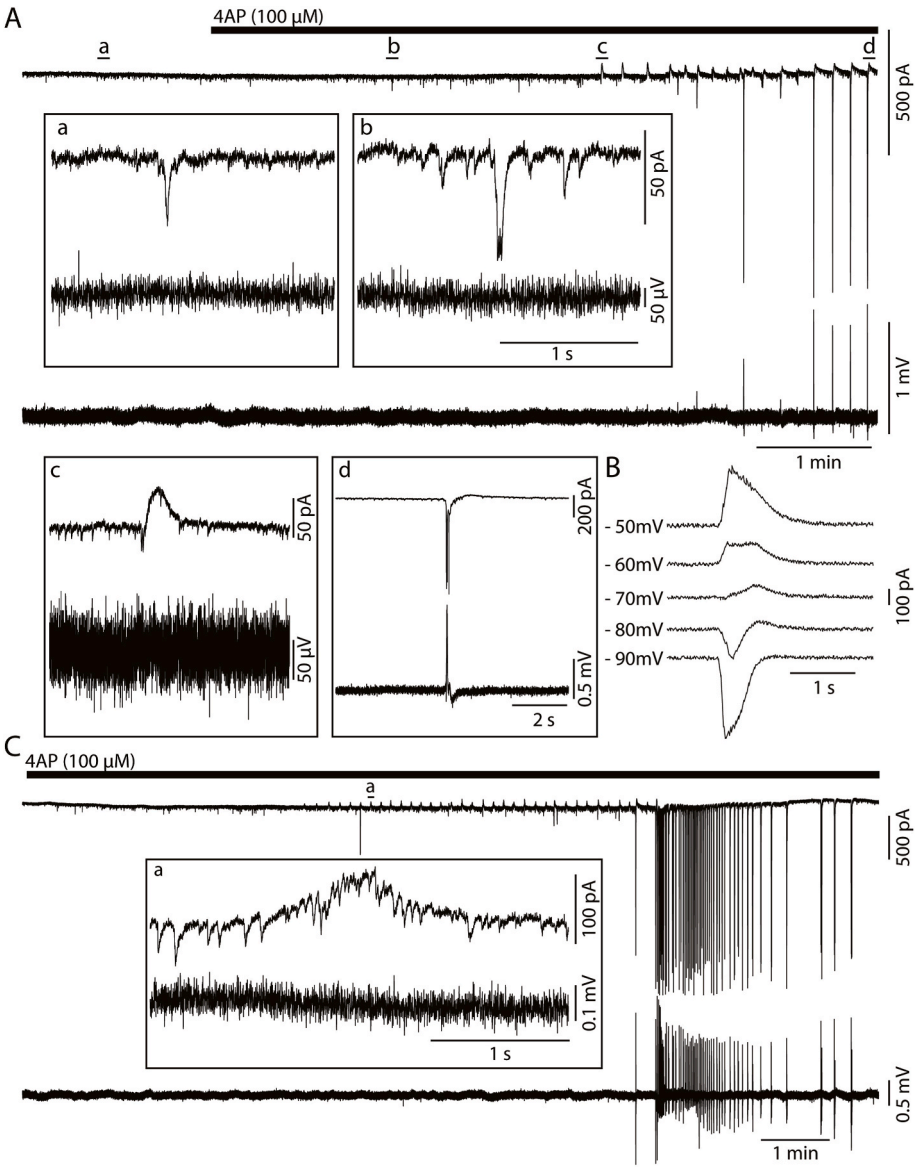

Fig. 1. Spontaneous slow outward currents in the CA3/4 region of the hippocampus under 4-aminopyridine. A: Representative trace showing voltage clamp recordings from a pyramidal neuron in CA3/4, under 4AP bath application (top trace of **A**, holding potential of -70 mV). Spontaneous EPSC before (**a**) and after (**b**) the application of 4AP. Spontaneous slow outward currents occurred under 4AP (**c**), followed by interictal-like activity (**d**). The bottom trace shows the corresponding field potential. **B**: Representative voltage clamp recording showing the reversal potential of the spontaneous slow outward currents. **C:** Example trace showing the occurrence of the spontaneous slow outward currents before ictal discharges under 4AP.

mM of KCl, 0.7 mM of $CaCl_2$, 3 mM of $MgCl_2$, 1.2 mM of NaH_2PO_4, 25 mM of $NaHCO_3$ and 8 mM of D-glucose (pH 7.25, 305 mOsm). The brain was quickly removed and coronal slices (thickness = 350–400 µm) were obtained in ice-cold (~4 °C) carbogenated (95% O_2 and 5% CO_2) choline chloride cutting solution using a vibratome (VT1000S; Leica, Wetzlar, Germany). Slices were then transferred and stored at room temperature (20–22 °C) in carbogenated (95% O_2 and 5% CO_2) artificial cerebrospinal fluid (ACSF) containing 125 mM of NaCl, 2.5 mM of KCl, 26 mM of $NaHCO_3$, 2 mM of $CaCl_2$, 2 mM of $MgSO_4$, 1.25 mM of NaH_2PO_4, and 10 mM of D-glucose (pH 7.4, 305 mOSM/kg). Slices were left to recover for at least 1 h at room temperature before starting the electrophysiological recordings. NBQX, 4AP, BMI and CGP55845 were purchased from Sigma-Aldrich, Oakville, ON, Canada. Drugs were dissolved in the ACSF and then applied to the brain slices.

Electrophysiological recording – Individual slices were then transferred to the recording chamber (RC-27L, Warner Instrument LLC, Hamden, CT) and perfused with ACSF (32–34 °C, 2–3 ml/min) for electrophysiological recordings. Neurons from the CA3/4 pyramidal layer were visualized with a Zeiss Axioscope microscope. Patch-clamp recordings in the whole cell configuration were performed with microelectrodes (1B150F-4; World Precision Instruments, Sarasota, Florida, USA, resistance 5–10MΩ) filled with a solution containing: 140 mM of KM_2SO_4, 6 mM of NaCl, 1 mM of $MgCl_2$, 10 mM of HEPES, 4 mM of Mg-ATP and 0.4 mM of Na_2-GTP (pH 7.25, 290 mOsm). Extracellular field potential recordings were performed from hippocampal CA3/4 pyramidal layer with a glass pipette (1B150F-4; World Precision Instruments, Sarasota, Florida, USA; resistance 1 MΩ) filled with ACSF. The distance between the patch and field potential pipettes ranged between 0.1 and 0.4 mm in different experiments. With the application of pharmacology, one cell per slice was patched. Any given pharmacological procedures was never repeated on the same slice. All signals were sampled at 5000 Hz, amplified with a high impedance Multiclamp 700A amplifier and digitized (Digidata 1322A, Molecular Devices, Palo Alto, CA, USA). PCLAMP software (Molecular Device) was used to record and visualize

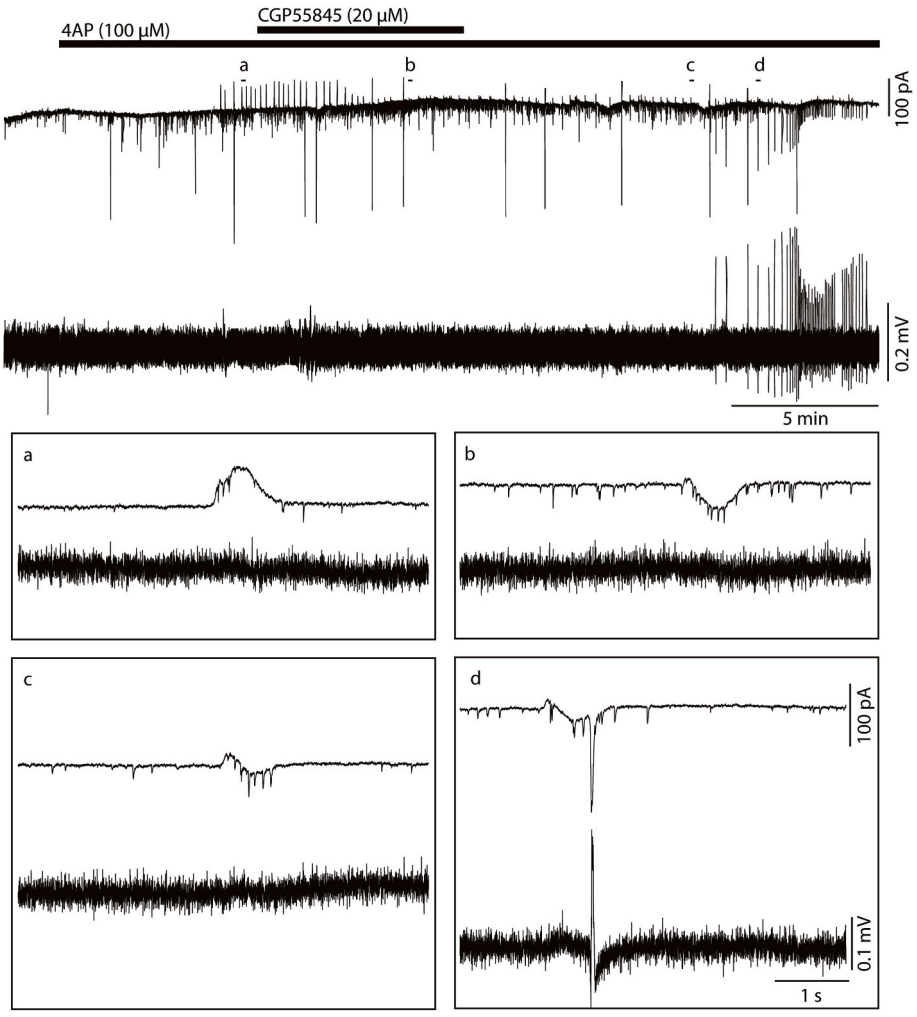

Fig. 2. CGP partially blocks spontaneous slow outward currents. A: Pyramidal neuron voltage clamp recording showing that application of CGP55845 under 4AP blocks spontaneous slow outward currents (holding potential of -70 mV). The bottom trace shows the corresponding field potential. Insets show a spontaneous slow outward current (**a**), the effect of CGP55845 (**b**), CGP55845 wash (**c**) and an interictal discharge (**d**).

the digitized data.

Data analysis and statistics - Custom Matlab (Version 9.9.0, Mathworks, MA, USA) scripts were written to visually analyze and quantify the data set. Electrophysiological traces were analyzed visually. Spontaneous slow outward currents during 4AP application were identified as events that were longer than 0.5 s without simultaneous field potential activity. The start of the spontaneous slow outward currents was identified as the first deflection from baseline while the end of the spontaneous slow outward currents was identified as the return to baseline; the peaks of the spontaneous slow outward currents was measured as the most positive point between the start and the end of the spontaneous events. Since data were not normally distributed, as established with the Kolmogorov-Smirnov test, non-parametric Kruskal-Wallis and Wilcoxon ranksum tests were used. The level of significance was set at $p < 0.05$. Statistical data are presented in the format of mean ± standard error of mean.

3. Results

4-aminopyridine induced outward currents – We applied 4AP (100 μM) to mouse brain slices while patching CA3/4 pyramidal neurons (holding potential = - 70 mV, n = 8 cells from 4 animals). Following 4AP application, spontaneous inward currents, which presumably represented a mixture of EPSCs and IPSCs, increased in amplitude within 1–1.5 min (Fig. 1Aa and b) and were then followed by a series of spontaneously occurring slow outward currents (duration = 1.004 s ± 0.048 s; amplitude = 75.64 pA ± 7.461 pA; interval = 7.123 s ± 0.776 s; 224 s ± 17.28 s after the application of 4AP) that were not mirrored by any corresponding field activity (Fig. 1Ac). These slow outward currents disappeared within 147 s ± 15.37 s, which corresponded to the appearance of inward currents that were related to interictal-like discharges in the field potential (Fig. 1Ad). As shown in Fig. 1B, the slow outward currents became inward when the holding potential was set to -90 mV, indicating a reversal potential around -80 mV, which is close to the reversal potential of K^+. In slices that showed ictal discharges (n = 3 cells from 3 animals), the spontaneous slow outward currents still preceded both ictal and interictal discharges (Fig. 1C).

CGP55845 blocks the transient outward currents - It is well established that K^+ outward currents can result from the postsynaptic activation of metabotropic $GABA_B$ receptors (Andrade et al., 1986; Dutar and Nicoll, 1988; Hill and Bowery, 1981; Newberry and Nicoll, 1985). Therefore, we applied the $GABA_B$ receptor antagonist CGP55845 (10–20 μM; n = 8 cells from 3 animals) after the appearance of these spontaneous slow outward currents (Fig. 2). CGP55845 abolished them (Fig. 2b) but spontaneous inward currents corresponding to interictal spikes in the field recordings still occurred (Fig. 2d; n = 6 cells from 3 animals). Notably, before the appearance of epileptiform activity, the spontaneous slow outward currents recorded under CGP55845 became mainly inward suggesting the disclosure of $GABA_A$ and glutamatergic inward components (compare insets a and b in Fig. 2).

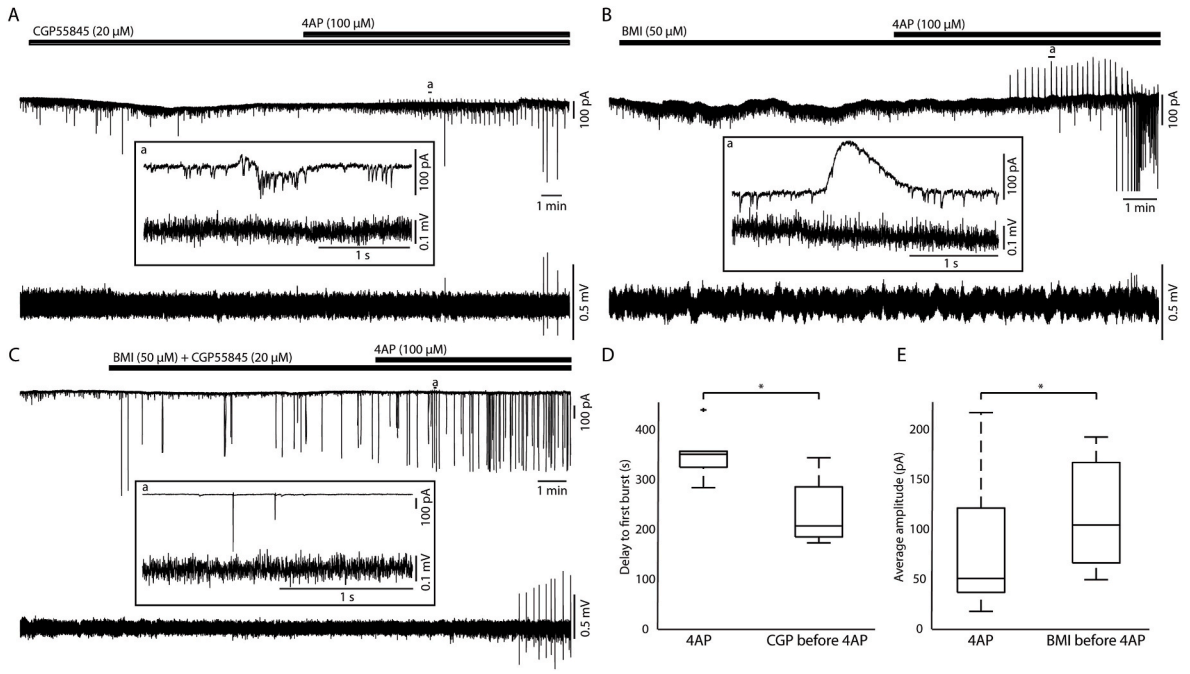

Fig. 3. – Slice pre-treatment bath application of CGP and BMI blocks the spontaneous slow outward currents. A: Voltage clamp recording from hippocampal CA3/4 pyramidal neuron (holding potential of -70 mV) showing that CGP55845 slice pre-treatment before 4AP application partially blocked the occurrence of spontaneous slow outward currents. The bottom trace shows the corresponding field potential. The inset shows the action of CGP55845 (**a**). **B**: Representative voltage clamp recordings (holding potential of -70 mV) showing that BMI pre-treatment before 4AP application has minimal effect on the occurrence of spontaneous slow outward currents. The bottom trace shows the corresponding field potential. The inset shows the effect of BMI on the spontaneous slow outward currents (**a**). **C**: Representative voltage clamp recordings (holding potential of -70 mV) showing that pre-treatment with CGP55845 and BMI before 4AP application completely blocked the occurrence of spontaneous slow outward currents. The bottom trace shows the corresponding field potential. The inset shows a representative inward current (**a**). **D**: Boxplots comparing the delay from the application of 4AP to the occurrence of the first inward burst with simultaneous field activity, between 4AP only and CGP55845 before 4AP. **E**: Boxplots comparing the amplitude of the slow outward currents between 4AP only and BMI before 4AP. For **D** and **E**, + indicates outlier data points while * indicates statistical significance ($p < 0.05$).

CGP55845 and bicuculline pre-treatment abolishes the outward currents - To confirm that the disappearance of spontaneous slow outward currents was due to the blockade of $GABA_B$ receptors rather than to an effect of time, we pre-treated the slice with CGP55845 before the application of 4AP (n = 4 cells from 4 animals). Under these conditions, and similar to the experiment shown in Fig. 2, only predominantly inward currents, without any corresponding field activity, were recorded (Fig. 3A). When we compared the delay between the application of 4AP to the occurrence of the first inward burst co-occurring with the interictal spike in the field, slices that were pre-treated with CGP55845 showed significantly shorter delay compared to 4AP only (Fig. 3D). In order to investigate the nature of these slow inward currents (see Figs. 2b and 3Aa), we pretreated the slice with the $GABA_A$ receptor antagonist bicuculline (BMI) before the application of 4AP and found no occurrence of slow inward currents while spontaneous slow outward currents were still present (Fig. 3B; n = 4 cells from 4 animals), which was likely due to their $GABA_B$ component that masks the inward component. Since we have shown that the $GABA_A$ component is mainly inward, we analyzed its amplitude under BMI pre-treatment. The amplitude of the slow inward currents were indeed significantly higher under BMI than the amplitude of the slow inward currents under 4AP only. We then pre-treated the slice with both CGP55845 and BMI before applying 4AP; this pharmacological procedure completely abolished both the slow outward and inward components (Fig. 3C; n = 7 cells from 3 animals) suggesting that both $GABA_A$ and $GABA_B$ receptor activation did contribute to the spontaneous slow outward currents.

Glutamatergic transmission controls the occurrence of outward currents - Since the spontaneous slow outward currents were substituted by inward currents corresponding to interictal spikes in the field, we hypothesized that the disappearance of the spontaneous slow outward currents was due to on-going, presumably potentiated, glutamatergic-mediated transmission. Therefore, we applied the highly selective competitive antagonist of AMPA and KA ionotropic glutamate receptors NBQX (10 μM) (Randle et al., 1992) before applying 4AP. NBQX successfully blocked the spontaneous EPSCs recorded before 4AP application (Fig. 4A; n = 24 cells from 12 animals). Moreover, under these pharmacological conditions, 4AP application disclosed spontaneous slow outward currents (Fig. 4Aa), which were partially blocked during subsequent CGP55845 application (Fig. 4Ab; n = 12 cells from 7 animals). We also applied NBQX after the disappearance of the slow outward currents under 4AP (Fig. 4B), which partially recovered the spontaneous slow outward currents (Fig. 4Bb; n = 2 out of 3 cells from 3 animals).

4. Discussion

In this study, we have identified, for the first time, the transient occurrence of spontaneous slow outward currents during the application of 4AP in mouse CA3 pyramidal neurons. These spontaneous, slow outward currents: (i) were mainly mediated by the presumptive, postsynaptic activation of $GABA_B$ receptors; (ii) did not represent synchronous network events since they were not mirrored by field activity; (iii) were followed by the occurrence of interictal and/or ictal discharges, suggesting that they were blocked by the subsequent synchronization of large populations of glutamatergic networks.

Previous experiments performed with rat hippocampal slices have shown that 4AP application induces an increase in rate and amplitude of both inhibitory and excitatory synaptic transmission (Buckle and Haas, 1982; Perreault and Avoli, 1991). Furthermore, slow IPSPs presumably mediated by K^+ currents were also observed under topical application of

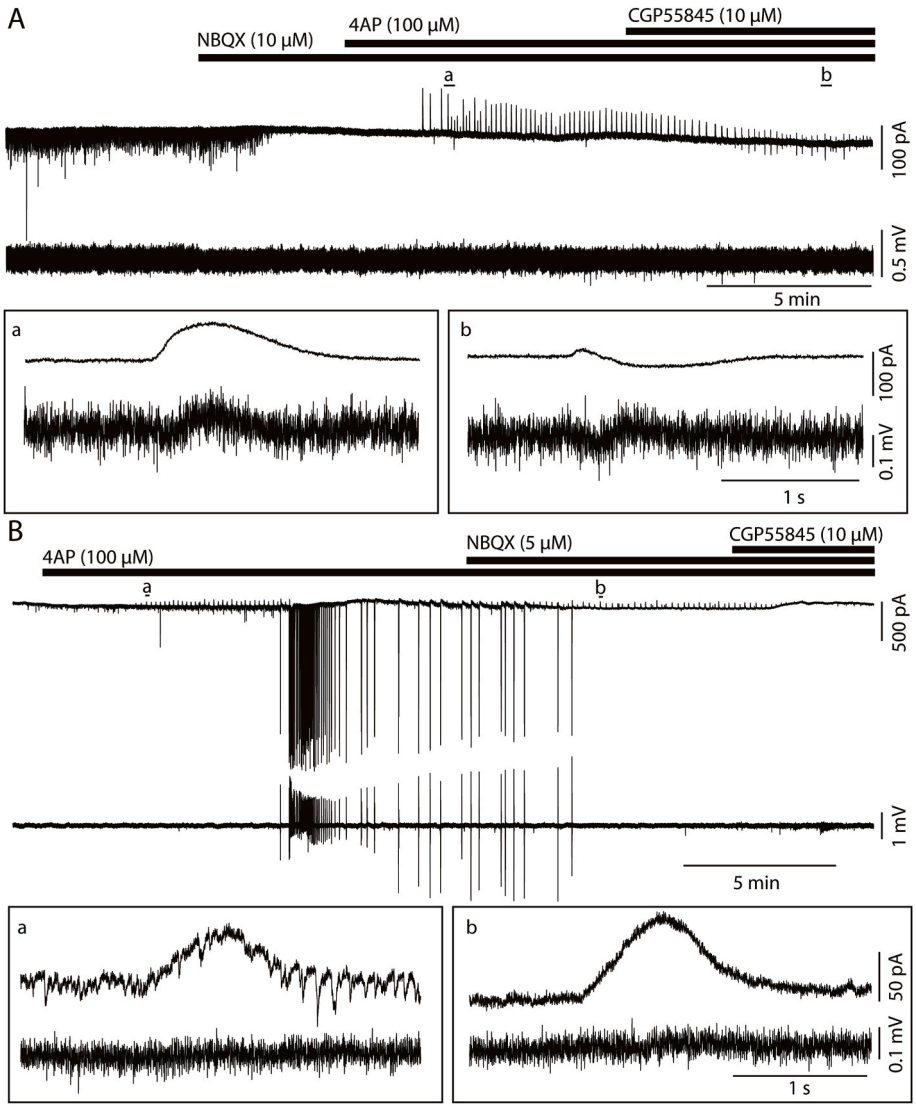

Fig. 4. NBQX and BMI failed to block the occurrence of spontaneous slow outward currents. A: Voltage clamp recording from hippocampal CA3/4 pyramidal neuron (holding potential at -70 mV) showing that pre-treatment with NBQX did not block the spontaneous slow outward currents induced by 4AP. Representative spontaneous slow outward currents under NBQX and 4AP in (**a**). The application of CGP55845 partially blocked their occurrence (**b**). **B**: Representative voltage clamp recordings (holding potential at -70 mV) showing that spontaneous slow outward currents partially recovered after NBQX application. Spontaneous slow outward currents under 4AP are shown in (**a**) and spontaneous slow outward currents under 4AP and NBQX are shown in (**b**).

4AP to the rat hippocampal CA1 region (Segal, 1987). In our experiments, we have observed slow IPSCs with voltage clamp recordings in mice hippocampal pyramidal neurons during the transition period between the application of 4AP and the occurrence of epileptiform discharges. These IPSCs were presumably the IPSPs observed during both bath (Perreault and Avoli, 1989) and topical application of 4AP (Segal, 1987) in hippocampal slices from rats.

In agreement with Segal (1987), we have observed that under bath application of 4AP, outward currents are due to the efflux of K^+ ions, since the reversal potential of outward currents was around – 80 mV (Hill and Bowery, 1981; Newberry and Nicoll, 1985). In addition, we found that these slow outward currents are mediated by metabotropic $GABA_B$ receptor activity (Andrade et al., 1986; Dutar and Nicoll, 1988) with some $GABA_A$ contribution. The slow dynamic of these outward currents is probably due to the metabotropic nature of $GABA_B$ receptors (Misgeld et al., 1995). Notably, the IPSP-EPSP sequences recorded by Perreault and Avoli (1989) are likely to be $GABA_A$ receptor and ionotropic glutamatergic receptor-mediated activities, since we have recorded similar activities under voltage clamp when $GABA_B$ receptors were blocked with CGP55845.

Several studies have demonstrated the role of $GABA_B$ receptors in epileptiform synchronization (see for review Avoli and Lévesque, 2022). Application of the $GABA_B$ receptor agonist baclofen under zero Mg^{2+} or during 4AP application was reported to block interictal discharges while disclosing ictal discharges (Scott Swartzwelder et al., 1987; Motalli et al., 1999). Moreover, it has been reported that antagonizing $GABA_B$ receptors with CGP35348 increases the occurrence of both interictal and ictal discharges (Motalli et al., 2002). Our findings reveal that following 4AP administration, $GABA_B$ receptors, which are presumably located post-synaptically on CA3 pyramidal cells, undergo a transient period of hyperactivation that cause large outward K^+ currents that are capable of masking simultaneously on-going $GABA_A$ and ionotropic glutamatergic currents in an asynchronized manner. These $GABA_B$ mediated outward currents were succeeded by inward currents and epileptiform discharges that appeared sooner when $GABA_B$ receptors were antagonised thus suggesting a potential role of $GABA_B$ receptor activation in reducing neuronal network synchronization and, consequently, blocking epileptiform discharges. We propose that such mechanism may represent a

future therapeutic target to reduce neuronal network synchronization and potentially alleviate epileptiform discharges in patients with temporal lobe epilepsy.

CRediT authorship contribution statement

Adriano Cattani: Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing, Visualization. **Siyan Wang:** Conceptualization, Methodology, Investigation, Software, Writing – original draft, Writing – review & editing, Visualization. **Maxime Lévesque:** Project administration, Writing – original draft, Writing – review & editing, Visualization. **Jean-Pierre Farmer:** Supervision, Writing – review & editing, Funding acquisition. **Roy William Roland Dudley:** Supervision, Writing – review & editing, Funding acquisition. **Massimo Avoli:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Visualization, Supervision, Resources, Funding acquisition.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Massimo Avoli reports financial support was provided by Canadian Institutes of Health Research. Roy William Roland Dudley reports financial support was provided by Foundation of the Department of Neurosurgery, McGill University. Massimo Avoli reports financial support was provided by Savoy Foundation Inc.

Data availability

Data will be made available on request.

Acknowledgments

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