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REVIEW

GABA WITHDRAWAL SYNDROME: $GABA_A$ RECEPTOR, SYNAPSE, NEUROBIOLOGICAL IMPLICATIONS AND ANALOGIES WITH OTHER ABSTINENCES

E. CALIXTO *

Departamento de Neurobiología, Dirección de Investigaciones en Neurociencias, Instituto Nacional de Psiquiatría "Ramón de la Fuente", Calzada México-Xochimilco No. 101, Tlalpan, 14370 México, D.F., Mexico

Abstract—The sudden interruption of the increase of the concentration of the gamma-aminobutyric acid (GABA), determines an increase in neuronal activity. GABA withdrawal (GW) is a heuristic analogy, with withdrawal symptoms developed by other GABA receptor-agonists such as alcohol, benzodiazepines, and neurosteroids. GW comprises a model of neuronal excitability validated by electroencephalogram (EEG) in which high-frequency and high-amplitude spike–wave complexes appear. In brain slices, GW was identified by increased firing synchronization of pyramidal neurons and by changes in the active properties of the neuronal membrane. GW induces pre- and postsynaptic changes: a decrease in GABA synthesis/release, and the decrease in the expression and composition of $GABA_A$ receptors associated with increased calcium entry into the cell. GW is an excellent bioassay for studying partial epilepsy, epilepsy refractory to drug treatment, and a model to reverse or prevent the generation of abstinences from different drugs. © **2015 Published by Elsevier Ltd. on behalf of IBRO.**

Key words: GABA, neuronal hyperexcitability, withdrawal.

Contents

GABA WITHDRAWAL SYNDROME (GWS), WHAT AND WHAT FOR?

Identification of the relationship between gamma-aminobutyric acid (GABA) and epilepsy allowed the quantification of a cortical hyperexcitability phenomenon caused by chronic treatment of GABA and the subsequent interruption of its administration in the brain cortex of monkeys. In an attempt to identify strategies to manage seizures caused by a genetic model of generalized epilepsy in the *Papio papio* mandrill (this epilepsy type is inducible because intermittent light stimulation gives rise to epileptiform discharges in the brain cortex, as well as generalized myoclonus; Brailowsky et al., 1989; Brailowsky, 1991a,b), it was observed that direct intracortical instillation of GABA was able to stop the appearance of seizures; in other words, GABA instillation exerted anticonvulsant effects that lasted until the end of the instillation (Brailowsky et al., 1988, 1989). However, the following day, after intracortical instillation of GABA, all of the monkeys exhibited paroxysmal electroencephalographic (EEG) activity at the sites where the instillation was performed.

Independent of the instillation site and the type of instillation cannula used, the EEG showed the presence of polyspike and spike–wave activity that, in the case of the motor cortex, was related with the appearance of myoclonus in the distal portion of the lower limbs; in other words, a different epileptiform activity appeared independent of the activity that the mandrill already

*Tel: +52-55-4160 5089; fax: +52-55-5655 9980.
E-mail address: ecalixto@imp.edu.mx

Abbreviations: AW, alcohol withdrawal; aloP, allopregnanolone; BLA, basolateral nucleus of the amygdala; DHEAS, dehydroepiandrosterone sulfate; DWS, Diazepam withdrawal syndrome; EEG, electroencephalogram; EPSP, excitatory post synaptic potentials; GABA, gamma-aminobutyric acid; GHB, β-hydroxybutyric acid; GAD, glutamic acid decarboxylase; GW, GABA withdrawal; GWS, GABA withdrawal syndrome; IP, intraperitoneal; LTP, long-term potentiation; NAcc, nucleus accumbens; NMDA, *N*-methyl-D-aspartate; PDS, paroxysmal depolarization shift; PS, pregnenolone sulfate.

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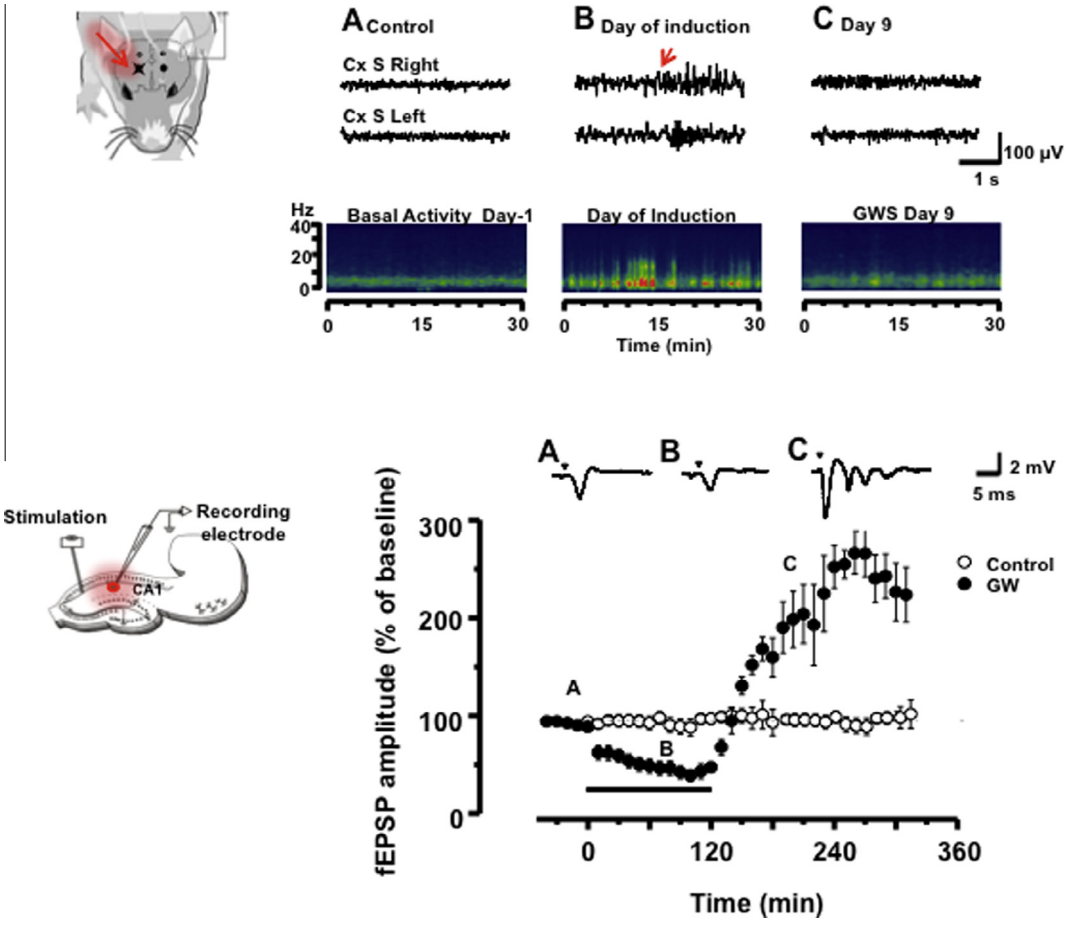

Fig. 1. Electrophysiological recordings of the hyperexcitability induced by gamma-aminobutyric acid (GABA) withdrawal syndrome (GWS) in two different models. GWS *in vivo*; upper panel, (A) recordings of the basal activity of the right and left somatomotor cortex of rats (upper and lower recordings, respectively). Wavelet analyses show the electroencephalographic (EEG) power of the right cortex. (B) Interruption of the intracortical instillation of GABA in the right cortex (5 mM/2 h) produces neuronal hyperexcitability; spike–wave activity is propagated to the contralateral hemisphere. An increase of power is identified in red colors in the Wavelet analysis. (C) The duration of this activity is about 7–8 days. At day 9 asymmetries in the EGG activity continue to be present; however, values are very similar to basal activity. *In vitro*; lower panel. Interruption of superfusion of GABA (5 mM/2 h) in brain slices of the hippocampus induces hyperexcitability (black circles). Temporal evolution and representative traces of the fEPSP are depicted in three different stages: before; during, and after GABA application (black bar). The increase of the amplitude of fEPSP, obtained from area CA1 of the hippocampus, is statistically significant at 30 min of GABA interruption. The effect is not reversible in the following 3 h. In contrast, the same stimulation frequency does not induce changes in the synaptic activity (control group; white circles; each symbol in the graphics represents the average ± standard error of the mean, SEM, of each group). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

demonstrated prior to treatment initiation (Brailowsky et al., 1990; Brailowsky, 1991a,b). Years later, hyperexcitability induction in neurons caused by GABA withdrawal (GW) was identified in epileptic rats subjected to amygdala kindling model and in non-epileptic rats. In these small mammals, it was possible to describe the behavioral and electroencephalographic characteristics of the phenomenon (Fukuda et al., 1987; Brailowsky et al., 1988; Brailowsky, 1991). This encouraged the use of rats in the model, from which the majority of the data have been obtained and which has permitted studying the phenomenology of the synaptic changes (Fig. 1).

ANATOMIC AND ENZYMATIC CHANGES OF GABAERGIC NEUROTRANSMISSION ON GW

Radioactive staining studies have permitted the identification of metabolic changes at the GABA instillation site and in subcortical structures connected through distance to the site where GW caused the neuronal hyperexcitability. Through the use of the 2-deoxyglucose (2-DG) radioactive capture/metabolism technique, it was possible to quantify a significant increase of local glucose consumption (from 3 to 5 times higher compared with the control) in the cortical area involved in the appearance of paroxysmal activity and in the ipsilateral thalamic zone of that cortical area (posterior, ventralis-lateral-posterior, ventralis-intermedius, ventralis-lateral, and reticularis oralis nuclei). These brain regions with oxidative metabolic increase correspond to reactive gliosis areas identified in the brains of animals obtained 10 days after the interruption of paroxysmal activity (Menini et al., 1991). These aspects are similar in temporal lobe epilepsy and in abstinence induced by Flunitrazepam or alcohol (Morrow et al., 2001; Olmedo and Hoffman, 2000;

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