REVIEW ARTICLE

The Long and Winding Road to Gamma-Amino-Butyric Acid as Neurotransmitter

Massimo Avoli, Krešimir Krnjević

ABSTRACT: This review centers on the discoveries made during more than six decades of neuroscience research on the role of gamma-amino-butyric acid (GABA) as neurotransmitter. In doing so, special emphasis is directed to the significant involvement of Canadian scientists in these advances. Starting with the early studies that established GABA as an inhibitory neurotransmitter at central synapses, we summarize the results pointing at the GABA receptor as a drug target as well as more recent evidence showing that $GABA_A$ receptor signaling plays a surprisingly active role in neuronal network synchronization, both during development and in the adult brain. Finally, we briefly address the involvement of GABA in neurological conditions that encompass epileptic disorders and mental retardation.

RESUMÉ: Le chemin long et sinueux pour que le GABA soit reconnu comme un neurotransmetteur. Cette revue est axée sur les découvertes réalisées durant plus de six décennies de recherche en neurosciences sur l'acide gamma-aminobutyrique (GABA) comme neurotransmetteur. À cet effet, nous mettons une emphase particulière sur le rôle significatif de chercheurs canadiens dans ce domaine de recherche. En prenant comme point de départ les premières études qui ont établi que le GABA était un neurotransmetteur au niveau de synapses centrales, nous faisons le sommaire des résultats identifiant le récepteur GABA comme étant une cible thérapeutique ainsi que des données plus récentes montrant que la signalisation du récepteur GABAA joue, de façon surprenante, un rôle actif dans la synchronisation du réseau neuronal, tant au cours du développement que dans le cerveau adulte. Finalement, nous traitons brièvement du rôle de GABA dans les maladies neurologiques incluant les troubles épileptiques et l'arriération mentale.

Keywords: Synaptic inhibition, neuronal synchronization, seizures, Cl^- transport, development, mental retardation.

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More than sixty years after the discovery that gamma-amino-butyric acid (GABA) is a major inhibitory transmitter in the brain, this article reviews its history, with special emphasis on the significant involvement of Canadian scientists. It is now well-established that GABA is the main inhibitory neurotransmitter in the adult forebrain.[1] Once released from interneuronal terminals, it activates pre- and postsynaptic GABA receptors, which are categorized into three types: A, B and C.[1,2] $GABA_A$ receptors activate ionotropic anionic channels while $GABA_B$ receptors are metabotropic, acting through second messengers. In addition, presynaptic $GABA_B$ receptors control transmitter release from excitatory and inhibitory terminals whereas such function remains controversial for $GABA_A$ receptors.[3] $GABA_C$ receptors, which activate ionotropic channels, are presumably confined to the retina in the adult,[4] though inhibitory functions in the adult hippocampus have been reported.[5]

$GABA_A$ receptors in various regions of the brain have different subunit compositions with specific functional and pharmacological characteristics.[6,7] Moreover, $GABA_A$ receptors are located both synaptically (low affinity) and extra-synaptically (high affinity), the latter being activated by spillover of synaptically released GABA; these two categories of receptors are believed to mediate phasic and tonic inhibition, respectively.[8-10] Our review is directed to the early steps that established the function of GABA as an inhibitory neurotransmitter[11] as well as on more recent evidence pointing to $GABA_A$ receptor signaling as a powerful mechanism underlying neuronal network synchronization both during development[12] and in the adult brain.[13] Indeed, several studies have identified a paradoxical synchronizing role played by $GABA_A$ receptors in cortical structures. Along this road we also discuss the ability of several clinically relevant drugs to modulate GABAergic function and the involvement of this neurotransmitter in neurological disorders.

ESTABLISHING GABA AS THE MAJOR INHIBITORY NEUROTRANSMITTER

The standard criteria for identification of a neurotransmitter are: (i) its presence in presynaptic neurons; (ii) its release from these presynaptic terminals following activation of these neurons; (iii) its ability to mimic the synaptic response when exogenously applied; and (iv) the ability of agonists or antagonists to enhance or block, respectively, both the response induced by presynaptic terminal activation and that evoked by application of

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the candidate substance.[14,15] It took nearly two decades for GABA to comply with these criteria. Almost simultaneously, in November 1950, three independent studies reported the presence of large amounts of GABA in amphibian and mammalian brains.[16-18] However, while GABA is readily obtained by alpha-decarboxylation of glutamic acid - the most prominent amino-acid in brain - as an omega amino-acid it cannot be used for the synthesis of proteins and peptides; its function, therefore, remained a matter of speculation for several years.

The first clarifying event came about when the Austrian zoologist Ernst Florey happened to test mammalian brain extracts on the crayfish abdominal stretch receptors.[19] Powerful suppression of the spontaneous firing of the receptor neuron led Florey to conclude that the brain extracts contained a very effective inhibitory agent, which he appropriately named Factor I. To identify the chemical nature of Factor I, he came to Montreal, where there followed several major developments. Working in KAC Elliott's neurochemistry laboratory at the Montreal Neurological Institute, Hugh McLennan and Florey used the 'cortical cup' technique pioneered by Elliott and Jasper[20] to show that Factor I was released from the cat's brain *in situ* [21] and that topical applications of Factor I could depress transmission both in sympathetic ganglia and in the lumbar spinal cord.[21,22] Subsequently, after an exhaustive search for active brain constituents, Elliott's group concluded that GABA accounted for most of Factor I inhibitory action on the crayfish receptor neuron.[23,24] In support of a functional role for GABA came several studies by Herbert Jasper: first, showing depressant effects of GABA on spontaneous spindle waves and evoked potentials obtained with electroencephalogram (EEG) recordings from the cerebral cortex;[25] and then that the release of GABA from the cortex consistently varied with electrographic activity.[26,27]

In other respects, further progress was anything but straightforward. In Canada, two of the leaders in the field, Florey and McLennan, found reason to believe that Factor I and GABA were not identical.[28] In Australia, following up on these authors' earlier report demonstrating that Factor I inhibits transmission in the spinal cord, Curtis et al. applied GABA by iontophoresis from micropipettes to a variety of neurons in the feline spinal cord.[29] GABA (and some related amino acids) consistently depressed neuronal activity; however, for a number of reasons – including the apparent lack of an inhibitory post-synaptic potential (IPSP)-like hyperpolarizing action and resistance to antagonism by strychnine, known as an effective blocker of spinal inhibition - they concluded that the effects of GABA action were non-specific. A few years later, however, a similar iontophoretic approach, testing single units in the neocortex and cerebellum, led Krnjević and Phillis to propose that GABA was most likely to be the inhibitory transmitter in the brain.[30] This view was soon supported by the demonstration that (i) the GABA content of individual synaptosomes was sufficient to inhibit cortical cell firing[31] and (ii) stimulation of the neocortex[27] or cerebellum[32] caused GABA release. Compelling evidence for GABA's role as inhibitory transmitter came with the demonstration that its effects, when iontophoretically applied to cortical[33,34] cuneate[35] and Deiters neurons[36], had characteristics (e.g., reversal potentials) similar to those of the IPSPs generated by these cells.

As further mentioned in the following sections, many convulsants act by blocking inhibitory transmission. Indeed, one of the best known, picrotoxin, had proved to be an effective blocker of Factor I and GABA's inhibitory action on the stretch receptor neuron[37,38] as well as on mammalian brain stem neurons.[39,40] Another Canadian, RH Manske - working at the National Research Council Laboratories in Ottawa - had previously discovered bicuculline, the more direct antagonist of GABA receptors, during his systematic investigations of plant alkaloids. In 1933, he identified an unknown compound in the root bulbs of the common Canadian spring flower, Dutchman's breeches (*Dicentra cucularia*), which he named bicuculline.[41] Testing samples of bicuculline provided by Manske, pharmacologists at the University of Toronto shortly after found that bicuculline was a powerful convulsant when administered to frogs and rabbits.[42] Nothing further happened with bicuculline until 1970 when, after testing various known convulsants, Curtis et al. reported that bicuculline not only blocked inhibition in the central nervous system (CNS) but was a very effective GABA antagonist.[43] Thus, by the early 1970s, GABA had become widely accepted as the principal inhibitory neurotransmitter, especially in the brain.[44]

GABA Receptors as Targets for Drugs

Having established the role of GABA as the main inhibitory transmitter at central synapses, researchers tried to identify the interactions occurring between this receptor and neurotropic drugs or endogenous substances. In the 1970s, several studies revealed that benzodiazepines could enhance GABAergic inhibition in the CNS,[45-47] and led to the identification of a benzodiazepine site in the GABA receptor.[48,49] At that time, it was still unclear whether GABA receptors consisted of structurally and functionally different subtypes: the metabotropic $GABA_B$ receptor was not discovered before the end of that decade.[50] Nonetheless, electrophysiological, biochemical and behavioral data clearly indicated that benzodiazepine ligands modulated ionotropic GABAergic function. Subsequent molecular and pharmacological studies demonstrated an allosteric 'benzodiazepine site' on most α subunit-containing $GABA_A$ receptors.[51]

Over the last four decades, additional agents have been shown to modulate $GABA_A$ receptor function and it appears that these actions depend on separate binding sites.[51] These include, barbiturates (which depress neuronal activity and, at higher doses, may have a direct action on the $GABA_A$ receptor),[52-57] steroid metabolites[58] and neurosteroids,[59,60] ethanol[61-63] as well as propofol.[64]

Decreasing GABA Function Leads to Epileptiform Activity and Seizures

In 1954, two independent groups reported seizures in infants fed with a formula that was accidentally deficient in pyridoxine (also known as vitamin B6); pyridoxine is the coenzyme for the synthesis of GABA from glutamic acid via the enzyme glutamic acid decarboxylase.[65,66] Further studies showed that GABA prevented seizures and that drugs interfering with GABA synthesis could induce convulsions.[67,68] This evidence was later corroborated by experiments aimed at identifying the cellular and pharmacological mechanisms underlying epileptiform synchronization. First, it was shown that drugs capable of inducing focal interictal-like discharges preparations *in vivo*[69,70] and *in vitro*[71] were $GABA_A$ receptor antagonists, and that the occurrence of this type of epileptiform activity was characterized by reduction in recurrent and/or feed-forward inhibition.[72,73] Second, it was reported that the onset of electrographic seizures induced by

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repetitive activation of hippocampal inputs are associated with rapid fading of IPSPs.[74] Shortly later, Kostopoulos et al. found that cortical recurrent inhibition, which was maintained during an EEG pattern of generalized spike-wave discharge, became markedly reduced before the onset of electrographic tonic-clonic seizures.[75] Therefore, early in 1980s, weakening of $GABA_A$ receptor signaling was regarded by many neuroscientists as the main cause of seizure activity.

Role of GABA in Synchronizing Adult Neuronal Networks

Early intracellular recordings from thalamic relay cells *in vivo* highlighted the potential role of presumptive GABAergic IPSPs in causing what was known as rebound excitation, and ultimately leading to low frequency (7-14Hz) thalamocortical oscillations such as those associated with sleep spindles.[76,77] A major advance in understanding the mechanism of EEG spindles and the switch between waking and sleep came with the demonstration by Steriade's group at Laval University (Québec) that spindle generation depends on the activity of GABAergic inhibitory neurons in the reticular thalamic nucleus.[78,79] Along with the experiments performed *in vitro* by Llinas,[80] evidence obtained by several research groups during the last three decades have shown the importance of GABA receptor-mediated IPSPs for hyperpolarizing thalamocortical neurons at membrane potential levels that inactivate low-threshold Ca^{2+} conductances and activate the Ih current.[81-84]

Depolarizing effects of GABA were identified early in the spinal cord;[85,86] but $GABA_A$ receptor-activation was later observed in hippocampal pyramidal cells, most often following activation of receptors located on the dendrites.[87,88] These depolarizing effects were interpreted to reflect a higher concentration of Cl^- in the dendrites than in the soma of principal cells, where hyperpolarizations continued to be recorded.[89] Subsequent experiments have shown that $GABA_A$ receptor-mediated depolarizations in cortical neurons can also be generated by HCO_3^-, which also passes through the anionic channels that are opened during inhibition[90,91] but with an equilibrium potential more positive than for Cl^-.[92-94] The depolarizing effect of HCO_3^- and K^+ efflux and resulting gamma-frequency oscillations are sharply enhanced in the young hippocampus when carbonic anhydrase increases cytoplasmic HCO_3^-.[95] In addition, these $GABA_A$ receptor-mediated, HCO_3^--dependent depolarizations can also activate voltage-gated Ca^{2+} channels.[96]

As mentioned in the previous section, studies published between the 1950s and 1980s demonstrated that reducing $GABA_A$ receptor signaling can lead to seizures *in vivo* and interictal-like activity *in vitro*. This view was challenged by reports that epileptiform synchronization occurs during pharmacological conditions that do not interfere with $GABA_A$ receptor function and, in some cases, they appeared to enhance it.[13] Specifically, epileptiform discharges were observed during application of Mg^{2+} free-medium in concomitance with the preservation of IPSPs.[97,98] In addition, it was shown that cortical networks made hyperexcitable by reducing the function of specific K^+ channels could generate synchronous, propagating neuronal activity, even when ionotropic glutamatergic transmission was blocked.[99-102] It was also found that under these pharmacological conditions, each synchronous event was associated with elevations in extracellular potassium ion concentration ($[K^+]$).[103-105] Interestingly, shortly before, Mary Morris at the University of Ottawa had found in the hippocampal slice preparation that selective activation of $GABA_A$ receptors caused increases in extracellular $[K^+]$.[106] This finding was later elucidated in Kai Kaila's laboratory; specifically, it was shown that excessive activation of $GABA_A$ receptors leads to accumulation of Cl^- inside the postsynaptic cells and to a subsequent increase in K-Cl co-transporter (KCC2) activity that makes K^+ and Cl^- move to the extracellular space.[107]

GABA Receptor Signaling and High Frequency Oscillations

Synchronization of cortical interneurons also plays a critical role in the generation of fast EEG oscillations in the mature CNS; these include beta-gamma (at 20–80Hz) and high frequency oscillations (>80Hz, so called ripples).[108] Both beta-gamma rhythms and ripples - which are recorded from several cortical structures including those of the limbic system[109-112]- are implicated in higher brain processes such as attention, sensorimotor integration, consciousness, learning and memory.[113,114] *In vivo* studies have shown that ripples represent population IPSPs generated by principal neurons entrained by synchronously active interneuronal networks.[108,112,115]

Similar fast oscillations are reproduced *in vitro* by bath applying the cholinergic agonist carbachol, high-K^+, kainic acid, or metabotropic glutamate receptor agonists[116-119] as well as by electrical tetanic stimulation.[120,121] These studies showed that fast activities reflect the synchronization of inhibitory GABAergic networks,[122,123] with or without the contribution of excitatory glutamatergic networks and gap junctions.[124-126] The hypothesis that gamma oscillations reflect interactions within interneuron networks is also supported by computer modeling.[127,128]

GABA and Brain Maturation

$GABA_A$ receptor-mediated depolarizations in the developing CNS were first reported in rabbit hippocampus.[129] However, depolarizing $GABA_A$ receptor-dependent depolarizations were clearly established in immature brain tissue when Ben-Ari et al.[130] found giant $GABA_A$ receptor-mediated depolarizing potentials that were spontaneously generated by rat CA3 pyramidal cells during the first 12 days of postnatal life. It was later shown that, at least in rodents, these GABAergic potentials are consistently recorded during the first post-natal week and that, as the brain matures, they gradually change to hyperpolarization,[131,132] which is due to maturation of the outward Cl^- transporter KCC2.[95,133] In line with this view, synaptic response generated by glycine, which are also Cl^- mediated, change from depolarizing to hyperpolarizing during ontogeny.

GABAergic excitation in the immature CNS may play a role in the growth, differentiation, maturation and preservation of neurons as well as in establishing their synaptic connectivity during development.[12] These processes depend on Ca^{2+} influx that is presumably the main signaling system causing oscillations of cytoplasmic calcium ion concentration and activation of several Ca^{2+}-binding proteins. Since glutamatergic AMPA receptor-type pathways are not operative in the immature brain, $GABA_A$ receptor-mediated depolarizing currents in concert with those caused by activation of N-methyl-D-aspartate (NMDA) receptors, which are present quite early on, may cause significant Ca^{2+} influx.[12]

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GABA and Tonic Inhibition

Activation of high affinity $GABA_A$ receptors, localized extra- or perisynaptically, also causes tonic inhibition; these receptors have distinct, subunit compositions that include the δ α4, α5 and α6 subunits.[8-10,134-136] This tonic ('always on') current appears to be activated by taurine in the mouse ventrobasal thalamus, thus reducing the excitability of thalamocortical relay neurons.[137] Neurosteroids have been proposed to modulate preferentially tonic rather than phasic inhibition.[60,138-140] Indeed, neuroactive steroids may play a role in catamenial epilepsy and in temporal lobe epilepsy, as suggested by their ability to delay the establishment of this chronic condition following pilocarpine-induced status epilepticus in rodents.[141]

Over the last decade tonic currents have also been proposed to be involved in the potentiating effects of ethanol on $GABA_A$ receptor-mediated inhibition.[142] For instance, in the hippocampus, low concentrations of ethanol selectively augment the tonic inhibitory currents mediated by δ subunit-containing $GABA_A$ receptors.[143] In addition, it has been reported that chronic intermittent ethanol treatment causes a switch of its actions in the hippocampus from extrasynaptic to synaptic $GABA_A$ receptors.[144]

GABA and Neurological Disorders

Dysfunction of $GABA_A$ receptor signaling - such as loss or rearrangement of inhibitory interneurons, changes in subunit composition, intracellular ionic homeostasis, etc… - has been documented in several neurological conditions including epileptic disorders[145-147] and mental retardation conditions such as the Fragile X[148-150] and Down syndromes.[151-153] Because a relative excess of GABAergic inhibition may be a factor in conditions associated with memory loss such as aging,[152] the findings that both synaptic plasticity and long term memory can be rescued by agents reducing GABA-mediated inhibition[154-157] indicate potential lines of treatment.

To review all the studies published on these topics is beyond the purpose of this review. However, one should pay attention to the evolving concept of the role played by GABA under some specific pathological conditions such as the generation of seizures in epileptic patients and animal models. For instance, and contrary to expectations from evidence obtained in the 1970s by employing acute models of focal epileptiform discharges,[70] the onset of seizures recorded from epileptic patients undergoing presurgical electrophysiological investigations is characterized by marked reduction of unit firing.[158,159] In addition, recent data obtained from animal models of focal epilepsy, indicate that seizure onset is accompanied by increased activity of inhibitory interneurons that may, in fact, silence principal neurons.[160-162] This paradoxical role of inhibition in initiating seizures is in line with evidence obtained from several *in vitro* and *in vivo* acute studies that have demonstrated the participation of GABAergic, often depolarizing, currents in both the initiation and maintenance of prolonged periods of epileptiform synchronization.[13,163-167] The exact mechanisms by which $GABA_A$ receptor signaling facilitates seizure activity are still under scrutiny but evidence obtained *in vitro* from animal preparations[13,103,104] and slices of the human dysplastic cortex[147] point at increases in extracellular $[K^+]$ caused by GABA release from interneurons at the onset of seizure activity. It is indeed well established that elevating extracellular $[K^+]$ increases excitability and the occurrence of epileptiform discharges both *in vivo* and *in vitro*.[168-171] Evidence that $GABA_A$ receptor signaling can promote seizures may explain the disappointingly limited efficacy of antiepileptic drugs designed to potentiate GABA receptor-mediated inhibition.

Concluding Remarks

GABA has not ceased to surprise us. Throughout the brain, it is present in, and released from a variety of inhibitory neurons with different characteristics, and it acts on an even greater variety of receptors. Indeed, such major brain structures as the cerebellar cortex and the striatum consist of mostly GABAergic neurons on which depends efficient locomotion. However, albeit well-established, GABA's inhibitory function can differ greatly according to the type and composition of the targeted receptors and is, moreover, astonishingly malleable. Not only is it susceptible to modulation by a rich variety of drugs - many of which are in extensive clinical use – but, in addition, is characterized by a quite unexpected plasticity, arising from its membrane action, the activation of anionic channels; whether the action is mainly inhibitory or excitatory depends on the predominance of the relative contributions of chloride and bicarbonate ions, and of course the transmembrane Cl^- gradient, determined either locally or generally by the direction of net Cl^- transport; all these factors are indeed subject to genetic, developmental and pathological changes. These characteristics help to explain why GABA dysfunction is manifested in so many different ways by neurological patients.

Disclosures

Massimo Avoli and Krešimir Krnjević do not have anything to disclose.

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