GABAB Receptors in Neurodegeneration

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Chapter 10

$GABA_B$ receptors in neurodegeneration

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Abstract

GABA is the main inhibitory neurotransmitter in the mammalian central nervous system (CNS), and acts via metabotropic $GABA_B$ receptors. Neurodegenerative diseases are a major burden and affect an ever increasing number of humans. The actual therapeutic drugs available are partially effective to slow down the progression of the diseases, but there is a clear need to improve pharmacological treatment thus find alternative drug targets and develop newer pharmaco-treatments. This chapter is dedicated to reviewing the latest evidence about $GABA_B$ receptors and their inhibitory mechanisms and pathways involved in the neurodegenerative pathologies.

Keywords: neurodegenerative diseases, $GABA_B$ receptors, Alzheimer's disease, Parkinson's disease, temporal lobe epilepsy, hippocampal sclerosis.

10.1 Introduction

The $GABA_B$ receptor is the main inhibitory receptor in the mammalian brain (Curtis, 1974; Krnjevic, 1974). It was first described by Bowery et al. (1980) who used pharmacology techniques to identify it, but for almost 20 years afterwards no other study succeeded in confirming the presence of this receptor. In 1997 Kaupmann et al. characterized the sequence of the receptor gene, transcript, protein, and the molecular structure of the receptor. They also demonstrated the presence of alternative splice variants of the $GABA_B$ receptor; these were different in the N-terminus domain and named $GABA_{B1a}$ and $GABA_{B1b}$. One year later the same group (Kaupmann et al., 1998) and two others (Jones et al., 1998; White et al., 1998) demonstrated that this receptor was not fully functional in cells enriched with it, and they described a second $GABA_B$ receptor gene, transcript, protein, and the molecular structure of the mature fully functional receptor. These two proteins have therefore been defined as subunits of the fully functional receptor and given the names of $GABA_{B1}$ and $GABA_{B2}$. The same studies also demonstrated for the first time that, in order for a G-protein coupled receptor to be fully functional, it has to work as a dimer composed of these two subunits. In a short period of time other subunits were described (Isomoto et al., 1998) but with very minor roles and very low expression.

After the molecular characterisation of the two main subunits, DNA or RNA probes and antibodies became available, or could be produced in order to study the distribution, and the level of expression of both the proteins and the transcripts. Thus, many groups began to investigate distribution and expression levels of the $GABA_B$ receptors. Many of these studies were focused in specific areas of the brain and spinal cord in rodents, primates and in humans. Animal models of various neurodegenerative diseases were used in order to shed light on the structure, expression, and physiological and pathological roles of $GABA_B$ receptors in these conditions.

Electrophysiological and pharmacological evidence demonstrated abnormalities of the $GABA_B$ receptor in many pathological conditions such as spasticity, epilepsy, anxiety, depression and cognitive deficits (Marescaux et al., 1992; Mott et al., 1991, Olpe et al., 1993; Meeren et al., 2002; Stewart et al., 2009; Gassmannn and Bettler 2012; Castelli and Gessa, 2016). Further, more recently, involvement of the $GABA_B$ receptor has been demonstrated in neurodegenerative diseases such as Alzheimer's (Dal Prà, et al., 2019; Tang, 2019), amyotrophic lateral sclerosis (Schumacher, et al., 2019), Huntington's (Rosas-Arellano, et al., 2018; Rekik, et al., 2011) Parkinson's (Hillman, et al., 2012), essential tremors (Paris-Robidas, et al., 2012) and autoimmune encephalitis (Moser, et al., 2018; Maureille, et al., 2019). In this chapter the attention is focused on the role that $GABA_B$ receptors play in epilepsy, and, more specifically, temporal lobe epilepsy associated with hippocampal sclerosis TLE-HS. Attention is also given to two major neurodegenerative diseases, Alzheimer's (AD) and Parkinson's disease (PD).

10.2 $GABA_B$ receptor and its effects

It is well known that $GABA_B$ receptors belong to the G-protein coupled (guanine nucleotide binding protein) receptor family (Wojcik and Neff, 1984; Hill et al., 1984; 1985; Karbon and Enna, 1985; Andrade et al., 1986) and thus, are associated with slow synaptic neurotransmission. $GABA_B$ receptors were initially identified by their insensitivity to the $GABA_A$ antagonist bicuculline and their selective activation by (-)baclofen (Hill and Bowery, 1981). Later, a number of compounds specific for $GABA_B$ receptors were identified, e.g., the antagonist 2-hydroxy-saclofen and the class of antagonists named CGP. Activation of $GABA_B$ receptors produces three major effects: (a) increases in postsynaptic neuronal K^+ conductance to generate long-lasting inhibitory postsynaptic potentials (Dutar and Nicoll, 1988); (b) inhibition of adenylate cyclase activity, leading to a reduction in cAMP levels (Wojcik and Neff 1984; Hill 1984, 1985; Karbon and Enna, 1985; Andrade et al., 1986; Rascol et al., 1989); (c) decrease of membrane Ca^{2+} flux $GABA_B$ receptor activation mediated by G-proteins that are members of the pertussis toxin-sensitive family $G_{i\alpha}/G_{o\alpha}$ (Odagaki et al., 2000; Odagaki and Koyama, 2001). These actions are discussed separately below. More details about the history and structure of the $GABA_B$ receptors can be found in Chapters 1 and 2, respectively.

10.2.1 K^+ channels

When activated by an agonist, $GABA_B$ receptors increase K^+ conductance, producing hyperpolarisation of the cell membrane, which has been reported in various brain regions including the cortex (pyramidal cells; Connors et al., 1982; Karlsson and Olpe, 1989; Luhmann and Prince, 1991), hippocampus (granule cells and interneurons; Fujita, 1979; Misgeld et al., 1984; Dutar and Nicoll 1988a; Williams and Lacaille, 1992), cerebellum (Schreurs et al., 1992; Vigot and Batini, 1997), amygdala (Rainnie et al., 1991) and thalamus (Hirsch and Burnod, 1987; Crunelli and Leresche, 1991; Dossi et al., 1992).

It has been reported that in K^+ subunit deletion, G protein-activated inwardly rectifying potassium (GIRK) channel 2 (GIRK2) mutant mice, in hippocampal neurons, postsynaptic K^+ currents induced by the $GABA_B$ receptor agonist baclofen are reduced or absent, and it was demonstrated that deletion of GIRK2 did not involve presynaptic inhibition. Therefore, GIRK-containing channels were shown not to be responsible for presynaptic effects (Lüscher et al., 1997). In contrast, a K^+ current is shown to be coupled to $GABA_B$ receptors on presynaptic

terminals in hippocampal cultures (Thompson and Gähwiler, 1992), so changes in membrane K^+ flux appear to be due to postsynaptic $GABA_B$ receptor activation (Saint et al., 1990).

10.2.2 Ca^{2+} channels

Baclofen and GABA depress somatic Ca^{2+} currents not only in peripheral neurons (Dolphin and Scott, 1986; 1987; 1990) but also in cultured mammalian hippocampal and cerebellar neurons (Huston et al., 1990; Wojcik et al., 1990; Pfrieger et al., 1994). $GABA_B$ receptor-mediated blockage of Ca^{2+} channels and coupling mechanisms are involved (Scott et al., 1991). A reduction of Ca^{2+} currents can be considered responsible for the depression of synaptic transmission by presynaptic $GABA_B$ receptors (Huston et al., 1990).
More recent evidence showed that presynaptic neurotransmitter release is indeed modulated by $GABA_B$ receptors through Ca^{2+} channels. Patch clamp measurements from a presynaptic terminal indicate that baclofen reduced Ca^{2+} currents, but had no effect on presynaptic K^+ currents and this was G-protein dependent (Takahashi et al., 1998).

10.2.3 Inhibition of adenylate cyclase

$GABA_B$ receptor agonists inhibit basal and forskolin-stimulated neuronal adenylate cyclase in brain slices (Knight and Bowery, 1996), through a G-protein dependent mechanism that results in a reduced level of intracellular cAMP. When $GABA_B$ receptors are activated, one α subunit is released from the G-protein and interacts with AC to inhibit cAMP formation. The G-protein involved has been demonstrated to be $G_{i\alpha}/G_{o\alpha}$, because ADP-ribosylation of the G-protein by pertussis toxin blocked any receptor interaction (Asano and Ogasawara, 1986; Xu and Wojcik, 1986). The βγ subunit of the G-protein interacts with K^+ and Ca^{2+} channels, and can potentiate β-adrenoreceptor-mediated cAMP production (Knight and Bowery, 1996), via cross talk mechanisms (Lefkowitz, 1992). More details about the physiology of $GABA_B$ receptors can be found in Chapter 3.

10.3 $GABA_A$ receptors

GABA acts also through $GABA_A$ receptors. $GABA_A$ receptors are ligand-gated Cl^- ion channels generating fast synaptic inhibition (Schofield, 1987; Smith, 1995). $GABA_A$ receptors can be pharmacologically distinguished by the competitive antagonist bicuculline, they are modulated by many therapeutic agents, such as benzodiazepines (BZD), and are a potential drug target for a number of neurological disorders. $GABA_A$ receptors are widely distributed in the CNS (Fritschy and Möhler, 1995). The existence of multiple $GABA_A$ receptor subunits has been demonstrated by regional differences in affinity and distribution of binding sites for BZD receptor ligands (Niddam et al., 1987; Sieghart et al., 1987; Bureau and Olsen, 1990, 1993; Ruano et al., 1992).

10.4 $GABA_B$ in neurodegenerative diseases

Neurodegeneration is defined as the progressive atrophy and loss of function of neurons, which is present in neurodegenerative diseases. Neurodegenerative diseases are also characterized by deposition of proteins, due to a fault in post-translational processing, specifically defective proteolysis, leading to overproduction of misfolded proteins. There are several such proteins that undergo incorrect post-translational processing; however, for the purpose of this chapter only the major proteins involved are considered: tau, amyloid-β (Aβ), and α-synuclein.

10.4.1 $GABA_B$ in Alzheimer's disease

Alzheimer's disease (AD), as mentioned above, is a neurodegenerative disease described for the first time in 1907 by the Bavarian physician and pathologist Alois Alzheimer (1864 – 1915). Unfortunately, since then, and over a century later, the prevalence of AD has tremendously increased. It is now the fifth most common cause of death globally. About 44 million people worldwide are living with dementia, 70% due to AD (Dumurgier and Sabia 2020). The main symptoms of AD are: loss of recent memory, disorientation to time and place, sometimes antisocial behaviour -"loss of inhibitions", lack of outward physical signs. The symptoms observed are due to the specific regions of the brain affected by neurodegeneration, which are the hippocampus and the cortex, where the loss of neurons becomes increasingly evident with the progression of the disease (Fig. 10.1). The hippocampus is the centre for processing and storing memories, and cortex is the centre for high cognitive function built on memories.

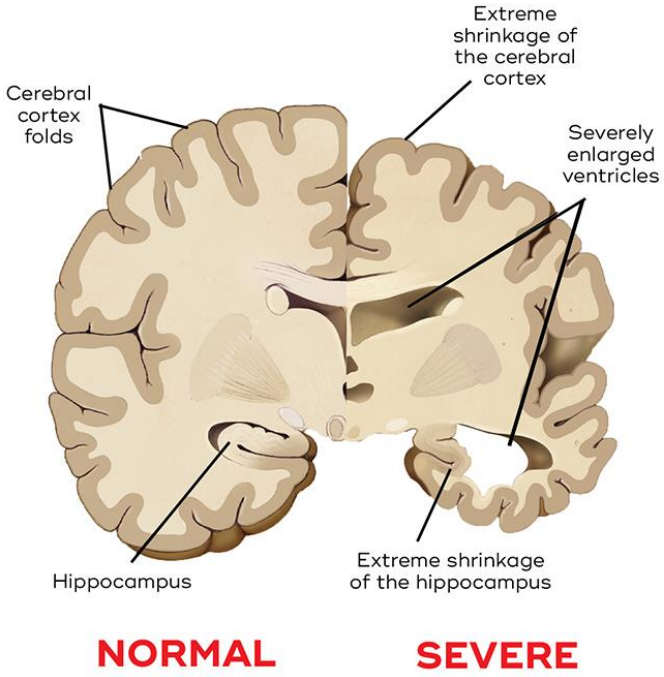

Figure 10.1. Brain imaging showing a control brain on the left and a brain affected by Alzheimer's disease on the right. (Credit: Queensland Brain Institute, The University of Queensland. qbi.uq.edu.au/dementia)

The neuropathological features of AD are extracellular senile plaques made up by amyloid-β protein, and intracellular neurofibrillary tangles (NFT) made up of paired filaments and hyper-phosphorylated tau protein (Fig. 10.2).

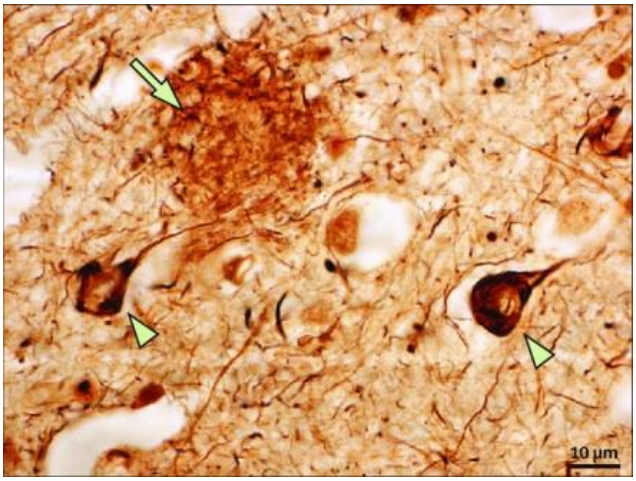

Figure 10.2. Neuropathological hallmarks of Alzheimer's disease. Post-mortem Bielschowsky silver staining of frontal cortex from a patient with Alzheimer's disease, showing the presence of a neuritic amyloid plaque (arrow), consisting of aggregated extracellular amyloid β fibrils, and intraneuronal neurofibrillary tangles (arrowheads), consisting of hyperphosphorylated tau protein. (Taken from Winblad et al., 2016 with permission from Elsevier journals License Number 4947750098122)

The majority of studies on AD are focused on the pathological processing of the amyloid precursor peptide (APP) leading to the formation of amyloid-β, the resulting build-up of amyloid plaques (Fig. 10.3), and also on the development of the tangles due to hyper-phosphorylation of the tau protein (Fig. 4). In addition to this, recent evidence has shown that $GABA_B$ receptors also play a role in the pathology of AD.

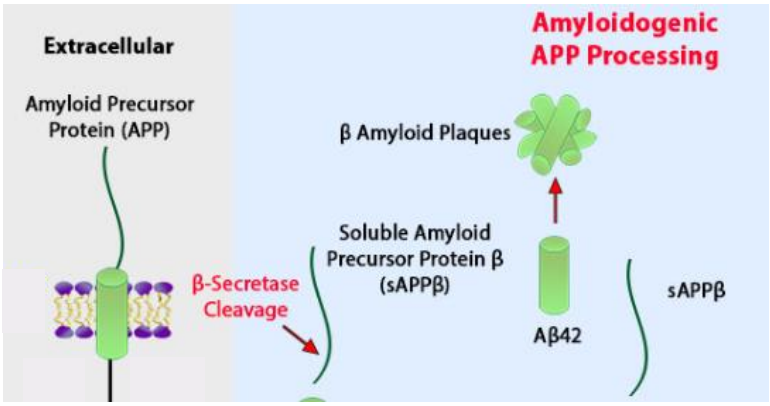

Figure 10.3. Schematic representation of the amyloid-plaque formation. Adapted from https://www.biolegend.com/amyloid_precursor_protein

The earliest indications for the role of $GABA_B$ receptors in AD emerged from a quantitative autoradiography binding study. In this study, a significant decrease of Bmax for $GABA_B$ receptors was reported in the cortex and hippocampus, especially in the *stratum moleculare* of the dentate gyrus (DG), the *stratum lacunosum-moleculare* and the *stratum pyramidale* of CA1 (Chu, et al., 1987a; b). Following up from these early findings, it was reported that, in a mouse model of colchicine-infused hippocampus, the sensory memory of the mice was impaired and also the amount of GABA in the cortex was decreased. Conversely, in mice simultaneously treated with colchicine and the $GABA_B$ antagonist CGP36742, memory loss was not recorded. The researchers of that study therefore concluded that the $GABA_B$

receptor antagonist CGP36742 could be a treatment for AD (Yu, et al., 1997). More experimental evidence obtained by immunohistochemistry emerged, corroborating the differential expression of $GABA_B$ receptors in varying stages of AD according to the Braak Staging. These data suggested that the expression of $GABA_{B1}$ is stable in CA1 through all the stages of the disease. In contrast, in the initial stages (Braak III/IV) of the pathology, the expression of $GABA_{B1}$ expression is higher in CA2-4, which could be interpreted as a compensatory (or self-defending) mechanism where the expression decreases with the progression of the disease (Braak V/VI), leading to neuronal death and impairment between excitation and inhibition. From these data it can be concluded that the formation of the NFTs in the hippocampus initially induces an increased expression and, later, increasing NFT accumulation stops the expression of this $GABA_B$ receptor specifically (Iwakiri, et al., 2005).

In recent data, rat *ex vivo* brain sections containing the hippocampus were treated with excess Aβ. These data demonstrated that, during the early stage of the disease, amyloid-β causes a dysregulation between excitatory and inhibitory neurotransmission, leading to disruption of the neuronal network. These changes are significant in the septo-hippocampal region, which processes learning and memory, according to oscillatory activity at the synapses between fimbria and CA3 (Nava-Meza et al., 2013). This group noted that the mechanism of action of amyloid-β was localised at the postsynaptic region and presumably linked to $GABA_B$ and its K^+ and Ca^{2+} channels via GIRK channels. These data suggest that amyloid-β modifies GIRK channels in CA3 pyramidal neurons in a way that is linked to the functioning of $GABA_B$ in the modulation of the hippocampal circuit. Another study on the effect of amyloid-beta (Aβ) on gene expression demonstrated that the level of expression of GIRK2, 3, and 4 subunits was decreased, but $GABA_B$ receptor expression was unaffected. These data corroborate the previous observations showing a relationship between the effect of Aβ and K^+ channels linked to $GABA_B$ receptors (Mayordomo-Cava, et al., 2015). Another study showed that in a rat streptozotocin-induced diabetic (STZ) model of sporadic AD, baclofen enhanced memory, again showing a role for $GABA_B$ receptors in AD (Pilipenko, et al., 2018). One of the latest pieces of evidence that $GABA_B$ receptors play a role in AD is the link between $GABA_B$/APP and the formation of Aβ, emerging from a study on sequence-related epitopes in APP with nanomolar affinity for the sushi-domain on the N-terminal site of presynaptic $GABA_{B1a}$ receptors. This study demonstrates, by using a proteomics approach, a multiprotein complex containing APP, c-Jun N-terminal kinase-interacting protein (JIP) and calsyntenin, together with $GABA_{B1a}$. This multiprotein complex facilitates Aβ formation and blocks the axonal trafficking of presynaptic of the $GABA_B$ receptor, decreasing its expression (Dinamarca, et al., 2019). In a genetic mouse model of AD expressing a chimeric mouse/human (Mo/Hu) APP-695 with mutations linked to familial AD (Oh, et al., 2009), the use of various immunohistochemical techniques demonstrated a decrease expression of $GABA_{B1}$ in the cell membrane surface of the *stratum lacunosum-moleculare* of CA1 pyramidal cells at 6 months of age. This reduced expression became more pronounced at 12 months of age and was coupled with an increase of the subunit in the intracellular compartment. Further, a reduction of $GABA_B$ receptors was observed in the axon terminal synapsing pyramidal CA1 cells (Martín-Belmonte, et al., 2020a). The same group demonstrated a significant decrease of $GABA_B$ receptors in the *stratum moleculare* of the DG, and also in axon terminals synapsing dendritic spines of granule cells, more evident in the outer than in the inner molecular layer (Martín-Belmonte, et al., 2020b).

All these data taken together, starting from the earliest indication (Chu, et al., 1987) up to the most recent data (Martín-Belmonte, et al., 2020a; b), indicate that $GABA_B$ receptors, and particularly $GABA_{B1a}$, have a decreased expression in the hippocampus. The reported reductions in $GABA_B$ expression are specific to the hippocampal subregions; however, it seems a general trend extended to CA1, CA3 and DG (which make up the trisynaptic circuit). Functionally, due to the decrease of $GABA_B$ receptors, there is an augmented production of Aβ, because the lack of $GABA_B$ receptors promotes the proteolysis of APP. This further supports the conclusions that $GABA_B$-mediated synaptic transmission is a major contributor in AD and $GABA_B$ receptors may be a suitable target for more effective drugs to treat AD. All these studies have focused their attention on $GABA_{B1}$, firstly because its expression was higher in the neuronal bodies and proximal dendrites where NFT accumulates in AD (Iwakiri et al., 2005). Secondly, $GABA_{B1a}$ has been demonstrated to form a complex with APP, whereas $GABA_{B1b}$ does not. Furthermore, the $GABA_{B1a}$ knock-out mice model showed a lack "of $GABA_B$ axonal transport and deficit in GBR-mediated inhibition of glutamate release". This model also showed that secreted APP functions as a $GABA_{B1a}$ ligand to modulate synaptic neurotransmission (Dinamarca et al., 2019; Martín-Belmonte et al., 2020).

10.4.2 $GABA_B$ in Parkinson's disease

Parkinson's disease (PD) is another neurodegenerative disease, described for the first time by James Parkinson (1817) in “An Essay on the Shaking Palsy”. PD is also known as *Paralysis Agitans*; it was first called Parkinson's disease by Jean-Martin Charcot in 1884. PD affects about 0.1-0.2% of the whole population. The incidence of the disease increases with age affecting 1% of people over 60 years of age. The main symptoms of PD are tremor at rest, muscle rigidity and bradykinesia. The symptoms observed are due to the specific region of the brain affected by the loss dopaminergic neurons: the substantia nigra (SN) (Fig. 10.4).

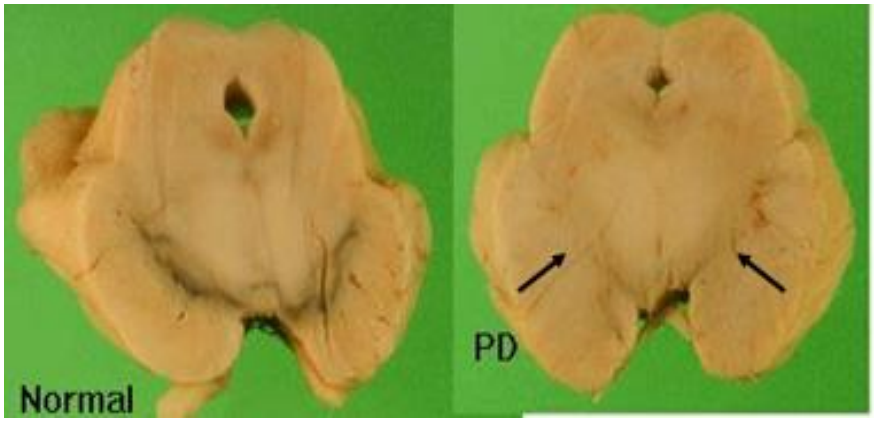

Figure 10.4. Brain images showing a normal postmortem sample on the left and the loss of pigmented neurons in the pars compacta of the substantia nigra (SNpc) of a postmortem PD patient on the right (black arrows).

The main neuropathological features are Lewy bodies, which contain α-synuclein (Fig. 10.5) in the SN and this is exhibited through impairment of voluntary movement (Braak, et al., 2003).

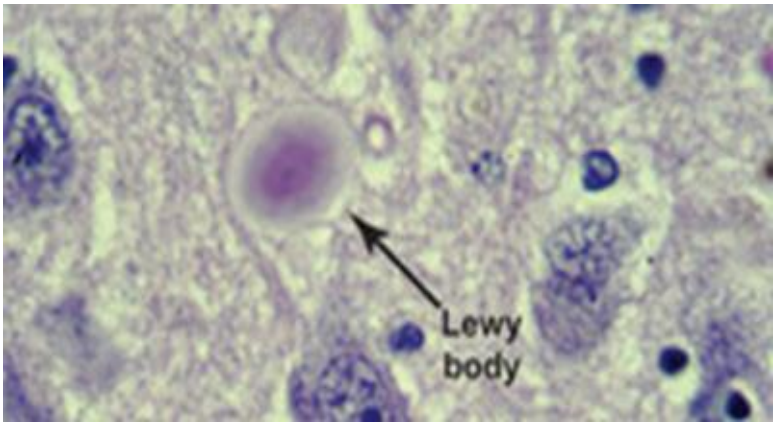

Figure 10.5. Photomicrographs showing the presence of Lewy bodies containing α-synuclein. Taken from https://www.alz.org/alzheimers-dementia/what-is-dementia/types-of-dementia/lewy-body-dementia

When the disease progresses these features spread to the cortex and neocortex (Tysnes, & Storstein, 2017). Figure 10.6 below illustrates the whole circuit and the inhibitory and excitatory connection.

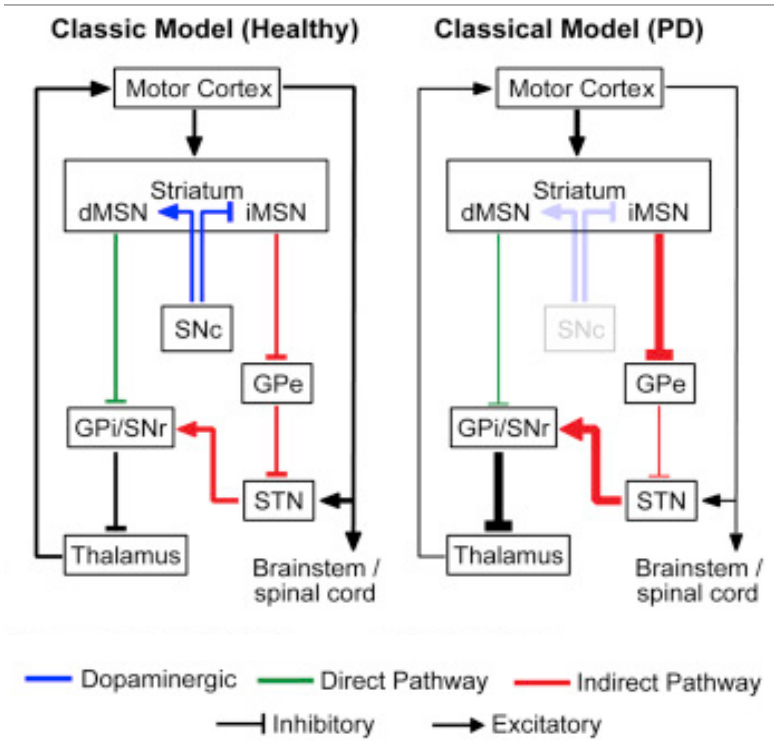

Figure 10.6. Schematic representation of the nigrostriatal circuit in the physiology and pathology of Parkinson's disease. Adapted from (McGregor, & Nelson, 2019; with permission).

When the dopaminergic neurons in the substantia nigra pars compacta (SNpc) start to degenerate, the dopaminergic signal to the caudate and putamen is reduced. The response

of the caudate and putamen therefore becomes modified, which results in an overall increase in the output of the interior Globus pallidus (GPi). This increase results in the inhibition of the thalamus. The thalamic excitatory signal to the motor cortex is diminished, thus causing reduced motor control. Also, the subthalamic nucleus (STN) plays a critical role in the regulation of movement, and abnormal activity of its neurons is associated with basal ganglia motor symptoms (McGregor, & Nelson, 2019).

The first evidence of involvement of $GABA_B$ receptors in PD emerged from electrophysiological recordings in neurons isolated from the Globus pallidus (GP) in the presence of baclofen. The data showed that the $GABA_B$-mediated effect was present only in one of the subtypes of GP neurons with a small soma, and the activation of $GABA_B$ modulated high-voltage-activated (HVA) calcium currents which may have an impact on the basal ganglia circuit (Stefani, et al., 1999). A 40% decrease in the expression of $GABA_B$ receptors in the SNpc and in the GPi was reported in a binding study utilising a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced PD monkey model (Calon, et al., 2000). The same group also demonstrated significant decreases in the mRNAs for $GABA_{B1}$ (-69%) and $GABA_{B2}$ (-66%) in the SNpc, and that the decreased expression of $GABA_{B1}$ mRNA was related to dopamine (DA) concentration (Calon, et al., 2001). The same group also analysed, via binding experiments, the expression of $GABA_B$ receptors in human post-mortem specimens and found a reduced binding in the putamen and external Globus pallidus (GPe) in PD patients compared with controls (Calon, et al., 2003). Also, in a rat model of PD with induced lesions of the nigrostriatal pathway, a reduction in $GABA_B$ mRNA was reported in the SNpc, whereas expression of the $GABA_{B1a}$ subunit was significantly increased in the substantia nigra pars reticulate (SNpr), entopeduncular nucleus, and the STN. Since these brain parts received reduced GABAergic innervation due to the lesion, this could indicate that the increased $GABA_{B1a}$ expression represents a compensatory mechanism (Johnston, & Duty, (2003). The fine-tuned localization of $GABA_{B1}$ receptors was investigated by Smith and colleagues (2000), who found an immunopositive signal in the striatopallidal complex in neuronal bodies and dendrites, striatal dendritic spine, axons and axon terminals. Analysis of $GABA_{B1}$ receptor distribution via immunogold electron microscopy showed extrasynaptic sites on dendrites, spines and somata in the striatopallidal complex, and perisynaptically at the synapses in the GP.

Whole-cell patch-clamp recordings were used to investigate tonic activation of $GABA_B$ receptors at pre- and post-synaptic levels, and the data indicated a major tonic activation of presynaptic $GABA_B$ receptors on the STN terminals compared to postsynaptic $GABA_B$ receptors on STN neurons. Therefore the presynaptic $GABA_B$ receptors could be considered as a new therapeutic target for treating some of the PD symptoms (Chen, & Yung, 2005).

It was later demonstrated through the frequency-dependent activation of postsynaptic $GABA_B$ receptors that the GP regulates the activity of the STN. These results clarify a novel way in which burst activity can be generated in the STN, and suggest that the effect of $GABA_B$ on STN neurons could generate abnormal burst activity in PD (Hallworth, & Bevan, 2005).

Further proof of the role that the $GABA_B$ receptor plays has come from studies in a rat model whereby the nigrostriatal pathway was depleted by treatment with 6-hydroxydopamine, and the rats were treated with the $GABA_B$ receptor antagonist CGP 56999A. The results showed

that the antagonist treatment attenuated the lack of DA in the rat striatum (Enna, et al., 2006).

A recently conducted investigation in an MPTP rat model demonstrated that baclofen reversed the effect of PD-like induced symptoms (Tyagi, et al., 2015). Another recent study in a mouse model of PD proved that the loss of GABAergic inhibition in the striatonigral connection led to motor impairment (Borgkvist, et al., 2015), corroborating once more the role of $GABA_B$ receptors in PD and moreover how it can be used as a potential drug target to treat certain parkinsonian symptoms.

It has long been established that DA plays a pivotal role in action selection and learning in the nigrostriatal pathway. However, any link between DA and $GABA_B$ receptors was not clearly defined until recently. The DA released into the striatum is influenced by local neurons, the majority of which are GABAergic, though it was not clear if it was a direct or indirect modulation via cholinergic innervation. Lopes and colleagues (2019) established that in the striatum GABA is capable of inhibiting release of DA via both ionotropic and metabotropic GABA receptors and that these actions are not mediated by acetylcholine. These results also demonstrated a tonic inhibition of DA release by striatal GABA, which occurs mainly via $GABA_B$ receptors. However, there is still lack of evidence of whether GABA receptors are expressed on DA axons (Lopes, et al., 2019).

Previously, the main neuropathological features of PD were mentioned: Lewi bodies containing α-synuclein and their accumulation in the intracellular space are major factors in the disease. Emmanouilidou et al., (2016) have examined the molecular pathway of α-synuclein secretion in mouse nucleus striatum and have found a new synaptic network that regulates α-synuclein release. They showed that α-synuclein secretion is a calcium-regulated mechanism depending on the activation of the sulfonylurea receptor 1 (SUR1), which is an inwardly-rectifying potassium ion channel Kir6 subunit that senses intracellular levels of the nucleotide ATP. They also demonstrated that modulation of GABA release through SUR1 located on GABAergic neurons controls α-synuclein release through activation of the presynaptic $GABA_B$ receptors. This study suggests that GABA transmission via SUR1 in mouse striatum modulates the α-synuclein secretory pathway, providing new insights for potential therapeutics to treat PD (Emmanouilidou, et al., 2016). Also, in a transgenic drosophila model carrying α-synuclein, it was shown that the transgenic flies lacked the capability of climbing, and this action was reversed by providing the drosophila with levodopa (L-DOPA_ or a $GABA_B$ (but not $GABA_A$) agonist in their food (Hillman, et al., 2012).

There have been useful studies directed toward clarification of various mechanisms underlying the pathophysiology of PD, of which those involving the role of $GABA_B$ receptors have been summarized above. Taken together, all the evidence available to date not only shows a fundamental role of $GABA_B$ receptors in PD, but also that via more recently described $GABA_B$ receptor innervation and modulation pathways there could be further potentials for better targeted therapies which may treat PD symptoms in a more effective manner.

10.4.3 $GABA_B$ in temporal lobe epilepsy

Different types of epilepsy are classified according to structural etiology referring to abnormalities visible on structural neuroimaging such as magnetic resonance imaging (MRI). The structural malformations may be acquired or genetic. The majority of focal seizures originate in the temporal lobes (Zentner, et al., 1995).

A well-known form of epilepsy linked with structural malformation is temporal lobe epilepsy associated with hippocampal sclerosis (TLE-HS). Temporal lobe epilepsy (TLE) is the most common form of focal epilepsy. About 6 out of 10 people with focal epilepsy have TLE. Seizures in TLE start in one point (*focus*) and then may involve both temporal lobes in the brain. TLE is subdivided in two types: mesial temporal lobe epilepsy (MTLE) and neocortical temporal lobe epilepsy (NTLE). MTLE encompasses the *medial* or internal structures of the temporal lobe. Seizures often begin in the hippocampus or surrounding area, and account for almost 80% of all temporal lobe seizures. NTLE encompasses the outer part of the temporal lobe. About 30-40% of patients affected by MTLE-HS are pharmaco-resistant (Engel, 2001). When seizures are prolonged and repeated they produce severe neuronal loss in the temporal lobe, mostly observed in the hippocampus, entorhinal cortex, amygdala and other brain areas (Van Paesschen, et al., 1997; Sutula and Hermann, 1999).

TLE-HS is not always considered or classified among the classical neurodegenerative diseases such as AD or PD. However, neurodegeneration in cornu ammonis (CA) subregions (Fig. 10.7), aberrant mossy fiber (MF) sprouting (Sutula et al., 1989), granule cell dispersion (Houser, 1990) and astrogliosis (Steinhäuser and Seifert, 2010) have been reported in the hippocampus in individuals with TLE-HS. Since the temporal lobe is a major cortical structure involved in learning and memory (Halgren, et al., 1991), recurrent spontaneous seizures (which are the primary triggering cause of TLE-HS) result in damage to this structure and therefore memory is impaired (Helmstaedter, 2002).

Neurodegeneration associated with TLE-HS has been observed in the human hippocampi (Fig. 10.7) and subsequently reproduced in rodent models. It is characterised by affecting the so-called trisynaptic circuit (Fig.10.8), specifically CA1 and CA3 subregions of the hippocampus, but not the CA2, DG, or subiculum; the neurodegeneration reported is also is associated with MF sprouting (Gloor, 1991; Sloviter, 1994).

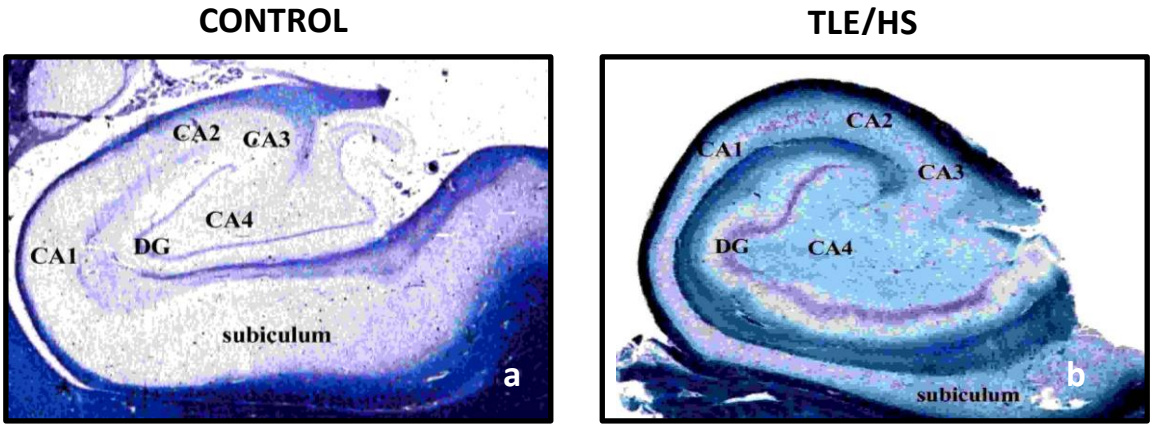

Figure 10.7. Cresyl violet/luxol fats blue stained sections of human hippocampus: a) control specimen; b) sclerotic specimen (not in scale). Taken from Princivalle PhD thesis (2003).

This neurodegeneration is accompanied by loss in GABAergic cells and altered expression of inhibitory receptor subunits in the DG and other parts of the hippocampal formation (Sperk, et al., 2004).

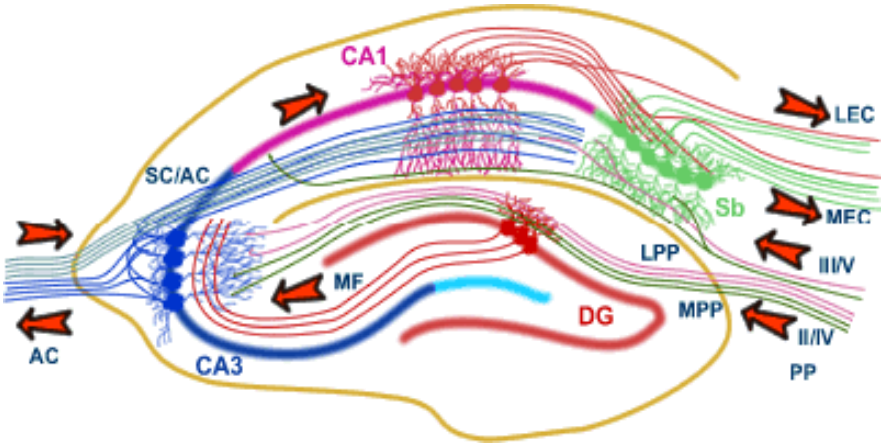

Figure 10.8. The hippocampal Network: The hippocampus forms a principally uni-directional network, with input from the entorhinal cortex (EC) that forms connections with the dentate gyrus (DG) and cornu ammonis CA3 pyramidal neurons via the perforant path (PP - split into lateral and medial). CA3 neurons also receive input from the DG via the mossy fibres (MF). They send axons to CA1 pyramidal cells via the Schaffer collateral pathway (SC), as well as to CA1 cells in the contralateral hippocampus via the associational commisural (AC) pathway. CA1 neurons also receive inputs directly from the PP and send axons to the Subiculum (Sb). These neurons in turn send the main hippocampal output back to the EC, forming a loop.
Taken from http://www.bristol.ac.uk/synaptic/pathways/

Inhibition mediated by GABA has been demonstrated to be reduced in neurons surviving hippocampal sclerosis (HS) associated with TLE (Mangan, et al., 1995; Mangan and Lothman, 1996). Evoked inhibitory post-synaptic potentials (IPSPs) in neurons from TLE-HS samples have been shown to be reduced compared with samples from patients with different structural lesions (Isokawa et al., 1991; Knowles et al., 1992).
In order to account for this finding, a number of research groups proposed different hypotheses for the decreased synthesis of GABA: (1) impairment in the GABA transporters (GAT) or the glutamate decarboxylase (GAD) enzyme, (2) reduced binding of GABA to the two receptor subtypes, $GABA_A$ and $GABA_B$, (3) reduced production of the receptors at transcriptional or translational level, or (4) post-translational modifications in the hippocampal area. More recent evidence emerged showing impairment in GABA (Thomas et al., 2003; 2005) and GABA transporters (Mathern, et al., 1999; Schijns, et al., 2015). Also $GABA_A$ receptor subunits were demonstrated to be differentially expressed in both in human TLE-HS hippocampal specimens (Loup, et al., 2006) and in animal models (Pirker, et al., 2003; Mazzuferi, et al., 2010), and in the amygdala and the entorhinal cortex of human patients (Stefanits, et al., 2019).

Most interesting for the purpose of this chapter is that anomalies in the expression of $GABA_B$ receptors have been reported both in human TLE-HS and animal models of it.
$GABA_B$ presynaptic receptor function has been demonstrated to be reduced in the DG granule cells of both kindled and kainate rat models of epilepsy (Buhl, et al., 1996; Haa, et al., 1996). Similar reduction was reported also in CA1 of partially (hippocampus)- or fully

(amYgdala)-kindled rats (Asprodini, et al., 1992; Wu, et al., 1997); none of these studies reported malfunctions in the $GABA_B$ recepotor-mediated post-synaptic potentials. However, Mangan and Lothman (1996) observed a reduction in both pre- and post-synaptic $GABA_B$ receptor function in CA1 neurons in a rat hippocampal-kindling model. The $GABA_{B1}$ and $GABA_{B2}$ transcript expression patterns have been reported in great detail in the rat (Kaupmann, et al., 1997, 1998; Munoz, et al., 1998; Bishoff, et al., 1999; Lu, et al., 1999; Benke, et al., 1999; Liang, et al., 2000; Jones, et al., 1998; Kuner, et al., 1999; Ng, et al., 1999; Clark, et al., 2000) and in human hippocampus (Berthele, et al., 2001; Princivalle, et al., 2003). The binding parameters of agonists and antagonists for $GABA_B$ receptors have also been reported extensively (Billinton, et al., 2001; Princivalle, et al., 2002; Furtinger, et al., 2003). $GABA_B$ receptors have been demonstrated to be differentially expressed in the hippocampus of TLE-HS in rat and mouse models, as well as in human specimens (Princivalle, et al., 2001; 2003; Nishimura, et al., 2005;Teichgräber, et al., 2009; Rocha, et al., 2015; Sheilabi, et al., 2017).
Electrophysiological evidence indicated that $GABA_B$ receptor expression may be an important factor for the onset of ictogenesis in the rat limbic system and, perhaps, in MTLE patients (Avoli 2004). Lang and colleagues (2014) demonstrated that $GABA_B$ receptors regulate hippocampal hyperexcitability by inhibiting CA3 glutamatergic synapses. They postulate that positive allosteric modulation of $GABA_B$ receptors may be effective in reducing seizure-related hyperexcitability. All these data demonstrate the loss of $GABA_B$ receptor function in TLE in rodents and humans.

The main common feature emerging from all these pieces of research evidence is that the physiological role of GABA and $GABA_B$ receptors is to induce hyperpolarization. Later on, however, it came up to light that GABA not only has an inhibitory action but could also have a depolarizing action, suggesting that GABA transmission is also involved in promoting epilepsy (Köhling, et al., 1998; Cohen, et al., 2002). In fact, Kantrowitz and colleagues (2004) demonstrated, by using electrophysiological techniques, that $GABA_B$ receptors regulate the synaptic depolarization to GABA response, and also that blocking of $GABA_B$ receptors with the specific antagonist CGP 55845A caused the depolarizing GABA response to become excitatory and pro-convulsive**.** Additionally, in very recent years it has been demonstrated in a mouse model of TLE that inhibition of presynaptic $GABA_B$ receptors has a depolarising action on cholecystokinin-positive basket cells [CCK(+) BCs], in the hippocampus, specifically in CA3 (Dugladze, et al., 2013).

All this body of evidence highlights the pivotal role that the $GABA_B$ receptor plays in TLE-HS, and the latest data particularly corroborate the importance that the reduced expression of $GABA_B$ receptors has in the pathophysiology of TLE. In the future, studies are needed to design, develop and test innovative drugs which can target $GABA_B$ receptors, specifically in the trisynaptic circuit.

10.5 Conclusions

It has long been recognised that GABA is the main inhibitory neurotransmitter in the mammalian brain and that it acts via the $GABA_A$ and $GABA_B$ receptors. This chapter has focused on the review of the role and mechanisms of action of $GABA_B$ receptors in three neurological diseases, which appear similar in some aspects and dissimilar in others. They are similar because they all show neurodegeneration; they are dissimilar because the

cerebral circuits involved in their pathophysiology are different in PD versus AD and TLE/HS, and because the main neuropathological features are different.
Altogether, the $GABA_B$ receptor plays a pivotal role in the inhibitory pathway in order to control the balance between excitatory/inhibitory signals in the trisynaptic circuit of the hippocampus, which has been described and demonstrated to have neuronal loss, in both AD and TLE/HS. On the other hand, in PD, $GABA_B$ has been shown to modulate excitatory/inhibitory signals via more newly described pathways different from the trisynaptic circuit.

Bibliography

Andrade, R., Malenka, R. C., & Nicoll, R. A. (1986). A G protein couples serotonin and GABAB receptors to the same channels in hippocampus. Science (New York, N.Y.), 234(4781), 1261–1265. https://doi.org/10.1126/science.2430334

Asprodini, E. K., Rainnie, D. G., & Shinnick-Gallagher, P. (1992). Epileptogenesis reduces the sensitivity of presynaptic gamma-aminobutyric acidB receptors on glutamatergic afferents in the amygdala. The Journal of pharmacology and experimental therapeutics, 262(3), 1011–1021.

Benke, D., Honer, M., Michel, C., Bettler, B., and Mohler, H. (1999). γ-Aminobutiric acid type B receptor splice variant proteins GBR1a and GBR1b are both associated with GBR2 in situ and display differential regional and subcellular distribution. J. Biol. Chem. 274, 27323-27330. doi:10.1074/jbc.274.38.27323

Berthele, A., Platzer, S., Weis, S., Conrad, B., & Tölle, T. R. (2001). Expression of GABA(B1) and GABA(B2) mRNA in the human brain. Neuroreport, 12(15), 3269–3275. https://doi.org/10.1097/00001756-200110290-00025

Billinton, A., Baird, V. H., Thom, M., Duncan, J. S., Upton, N., & Bowery, N. G. (2001). GABA(B) receptor autoradiography in hippocampal sclerosis associated with human temporal lobe epilepsy. British journal of pharmacology, 132(2), 475–480. https://doi.org/10.1038/sj.bjp.0703854

Bischoff, S., Leonhard, S., Reymann, N., Schuler, V., Shigemoto, R., Kaupmann, K., & Bettler, B. (1999). Spatial distribution of GABA(B)R1 receptor mRNA and binding sites in the rat brain. The Journal of comparative neurology, 412(1), 1–16.

Borgkvist, A., Avegno, E. M., Wong, M. Y., Kheirbek, M. A., Sonders, M. S., Hen, R., & Sulzer, D. (2015). Loss of Striatonigral GABAergic Presynaptic Inhibition Enables Motor Sensitization in Parkinsonian Mice. Neuron, 87(5), 976–988. https://doi.org/10.1016/j.neuron.2015.08.022

Bowery, N. G., Hill, D. R., Hudson, A. L., Doble, A., Middlemiss, D. N., Shaw, J., & Turnbull, M. (1980). (-)Baclofen decreases neurotransmitter release in the mammalian CNS by an action at a novel GABA receptor. Nature, 283(5742), 92–94. https://doi.org/10.1038/283092a0

Braak, H., Del Tredici, K., Rüb, U., de Vos, R. A., Jansen Steur, E. N., & Braak, E. (2003). Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiology of aging*, *24*(2), 197–211. https://doi.org/10.1016/s0197-4580(02)00065-9

Buhl, E. H., Otis, T. S., & Mody, I. (1996). Zinc-induced collapse of augmented inhibition by GABA in a temporal lobe epilepsy model. Science (New York, N.Y.), 271(5247), 369–373. https://doi.org/10.1126/science.271.5247.369

Bureau, M. H., & Olsen, R. W. (1993). GABAA receptor subtypes: ligand binding heterogeneity demonstrated by photoaffinity labeling and autoradiography. *Journal of neurochemistry*, *61*(4), 1479–1491. https://doi.org/10.1111/j.1471-4159.1993.tb13643.x

Bureau, M., & Olsen, R. W. (1990). Multiple distinct subunits of the gamma-aminobutyric acid-A receptor protein show different ligand-binding affinities. *Molecular pharmacology*, *37*(4), 497–502.

Calon, F., Morissette, M., Goulet, M., Grondin, R., Blanchet, P. J., Bédard, P. J., & Di Paolo, T. (2000). 125I-CGP 64213 binding to GABA(B) receptors in the brain of monkeys: effect of MPTP and dopaminomimetic treatments. Experimental neurology, 163(1), 191–199. https://doi.org/10.1006/exnr.2000.7366

Calon, F., Morissette, M., Rajput, A. H., Hornykiewicz, O., Bédard, P. J., & Di Paolo, T. (2003). Changes of GABA receptors and dopamine turnover in the postmortem brains of parkinsonians with levodopa-induced motor complications. Movement disorders : official journal of the Movement Disorder Society, 18(3), 241–253. https://doi.org/10.1002/mds.10343

Calon, F., Lavertu, N., Lemieux, A. M., Morissette, M., Goulet, M., Grondin, R., Blanchet, P. J., Bédard, P. J., & Di Paolo, T. (2001). Effect of MPTP-induced denervation on basal ganglia GABA(B) receptors: correlation with dopamine concentrations and dopamine transporter. Synapse (New York, N.Y.), 40(3), 225–234. https://doi.org/10.1002/syn.1045

Castelli, M.P., & Gessa, G.L. Distribution and Localization of the GABA B Receptor 2016 in "GABAB receptor"; Springer 1st ed. Springer Nature Switzerland AG. Part of Springer Nature. ISBN 978-3-319-46044-4

Chen, L., & Yung, W. H. (2005). Tonic activation of presynaptic GABA(B) receptors on rat pallidosubthalamic terminals. Acta pharmacologica Sinica, 26(1), 10–16. https://doi.org/10.1111/j.1745-7254.2005.00012.x

Chu, D. C., Penney, J. B., Jr, & Young, A. B. (1987a). Cortical GABAB and GABAA receptors in Alzheimer's disease: a quantitative autoradiographic study. Neurology, 37(9), 1454–1459. https://doi.org/10.1212/wnl.37.9.1454

Chu, D. C., Penney, J. B., Jr, & Young, A. B. (1987b). Quantitative autoradiography of hippocampal GABAB and GABAA receptor changes in Alzheimer's disease. Neuroscience letters, 82(3), 246–252. https://doi.org/10.1016/0304-3940(87)90264-3

Clark, J.A., Mezey, E., Lam, A.S., and Bonner, T.I. (2000). Distribution of the GABAB receptor subunit gb2 in rat CNS. *Brain Res*. **860**, 41-52. doi: 10.1016/s0006-8993(00)01958-2

Cohen, I., Navarro, V., Clemenceau, S., Baulac, M., & Miles, R. (2002). On the origin of interictal activity in human temporal lobe epilepsy in vitro. Science (New York, N.Y.), 298(5597), 1418–1421. https://doi.org/10.1126/science.1076510

Connors, B. W., Gutnick, M. J., & Prince, D. A. (1982). Electrophysiological properties of neocortical neurons in vitro. *Journal of neurophysiology*, *48*(6), 1302–1320. https://doi.org/10.1152/jn.1982.48.6.1302

Crunelli, V., & Leresche, N. (1991). A role for GABAB receptors in excitation and inhibition of thalamocortical cells. *Trends in neurosciences*, *14*(1), 16–21. https://doi.org/10.1016/0166-2236(91)90178-w

Curró Dossi, R., Paré, D., & Steriade, M. (1992). Various types of inhibitory postsynaptic potentials in anterior thalamic cells are differentially altered by stimulation of laterodorsal tegmental cholinergic nucleus. *Neuroscience*, *47*(2), 279–289. https://doi.org/10.1016/0306-4522(92)90244-v

Curtis D. R. (1974). Amino acid neurotransmitters and the brain. Beattie Smith lecture, March 28, 1974. The Medical journal of Australia, 2(20), 723–731.

Dal Prà, I., Armato, U., & Chiarini, A. (2019). Family C G-Protein-Coupled Receptors in Alzheimer's Disease and Therapeutic Implications. *Frontiers in pharmacology*, *10*, 1282. https://doi.org/10.3389/fphar.2019.01282

Dinamarca, M. C., Raveh, A., Schneider, A., Fritzius, T., Früh, S., Rem, P. D., Stawarski, M., Lalanne, T., Turecek, R., Choo, M., Besseyrias, V., Bildl, W., Bentrop, D., Staufenbiel, M., Gassmann, M., Fakler, B., Schwenk, J., & Bettler, B. (2019). Complex formation of APP with GABAB receptors links

axonal trafficking to amyloidogenic processing. Nature communications, 10(1), 1331. https://doi.org/10.1038/s41467-019-09164-3

Dolphin, A. C., & Scott, R. H. (1986). Inhibition of calcium currents in cultured rat dorsal root ganglion neurones by (-)-baclofen. *British journal of pharmacology*, *88*(1), 213–220. https://doi.org/10.1111/j.1476-5381.1986.tb09489.x

Dolphin, A. C., & Scott, R. H. (1987). Calcium channel currents and their inhibition by (-)-baclofen in rat sensory neurones: modulation by guanine nucleotides. *The Journal of physiology*, *386*, 1–17. https://doi.org/10.1113/jphysiol.1987.sp016518

Dolphin, A. C., & Scott, R. H. (1990). Activation of calcium channel currents in rat sensory neurons by large depolarizations: effect of Guanine nucleotides and (-)-baclofen. *The European journal of neuroscience*, *2*(1), 104–108. https://doi.org/10.1111/j.1460-9568.1990.tb00386.x

Dugladze, T., Maziashvili, N., Börgers, C., Gurgenidze, S., Häussler, U., Winkelmann, A., Haas, C. A., Meier, J. C., Vida, I., Kopell, N. J., & Gloveli, T. (2013). GABA(B) autoreceptor-mediated cell type-specific reduction of inhibition in epileptic mice. Proceedings of the National Academy of Sciences of the United States of America, 110(37), 15073–15078. https://doi.org/10.1073/pnas.1313505110

Dumurgier J, Sabia S. Nouvelles tendances épidémiologiques de la maladie d'Alzheimer [Epidemiology of Alzheimer's disease: latest trends]. Rev Prat. 2020 Feb;70(2):149-151. French. PMID: 32877124.

Dutar, P., & Nicoll, R. A. (1988). A physiological role for GABAB receptors in the central nervous system. *Nature*, *332*(6160), 156–158. https://doi.org/10.1038/332156a0

Engel J., Jr (2001). Finally, a randomized, controlled trial of epilepsy surgery. The New England journal of medicine, 345(5), 365–367. https://doi.org/10.1056/NEJM200108023450510

Enna, S. J., Reisman, S. A., & Stanford, J. A. (2006). CGP 56999A, a GABA(B) receptor antagonist, enhances expression of brain-derived neurotrophic factor and attenuates dopamine depletion in the rat corpus striatum following a 6-hydroxydopamine lesion of the nigrostriatal pathway. Neuroscience letters, 406(1-2), 102–106. https://doi.org/10.1016/j.neulet.2006.07.004

Emmanouilidou, E., Minakaki, G., Keramioti, M. V., Xylaki, M., Balafas, E., Chrysanthou-Piterou, M., Kloukina, I., & Vekrellis, K. (2016). GABA transmission via ATP-dependent K+ channels regulates α-synuclein secretion in mouse striatum. Brain: a journal of neurology, 139(Pt 3), 871–890. https://doi.org/10.1093/brain/awv403

Fisher RS, Cross JH, D'Souza C, et al. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia. 2017;58(4):531–542. doi:10.1111/epi.13671

Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58(4):522–530. doi:10.1111/epi.13670

Fritschy, J. M., & Mohler, H. (1995). GABAA-receptor heterogeneity in the adult rat brain: differential regional and cellular distribution of seven major subunits. *The Journal of comparative neurology*, *359*(1), 154–194. https://doi.org/10.1002/cne.903590111

Fujita Y. (1979). Evidence for the existence of inhibitory postsynaptic potentials in dendrites and their functional significance in hippocampal pyramidal cells of adult rabbits. *Brain research*, *175*(1), 59–69. https://doi.org/10.1016/0006-8993(79)90514

Furtinger, S., Pirker, S., Czech, T., Baumgartner, C., & Sperk, G. (2003). Increased expression of gamma-aminobutyric acid type B receptors in the hippocampus of patients with temporal lobe epilepsy. Neuroscience letters, 352(2), 141–145. https://doi.org/10.1016/j.neulet.2003.08.046

Gassmann, M., & Bettler, B. (2012). Regulation of neuronal GABA(B) receptor functions by subunit composition. Nature reviews. Neuroscience, 13(6), 380–394. https://doi.org/10.1038/nrn3249

GBD 2016 Dementia Collaborators (2019). Global, regional, and national burden of Alzheimer's disease and other dementias, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet. Neurology, 18(1), 88–106. https://doi.org/10.1016/S1474-4422(18)30403-4

Gloor P. Mesial temporal sclerosis: Historical background and an overview from a modern perspective. In: Lüders H, eds. Epilepsy Surgery. New York: Raven Press, 1991: 689–703.

Hallworth, N. E., & Bevan, M. D. (2005). Globus pallidus neurons dynamically regulate the activity pattern of subthalamic nucleus neurons through the frequency-dependent activation of postsynaptic GABAA and GABAB receptors. The Journal of neuroscience : the official journal of the Society for Neuroscience, 25(27), 6304–6315. https://doi.org/10.1523/JNEUROSCI.0450-05.2005

Haas, C. A., Deller, T., Naumann, T., & Frotscher, M. (1996). Selective expression of the immediate early gene c-jun in axotomized rat medial septal neurons is not related to neuronal degeneration. The Journal of neuroscience : the official journal of the Society for Neuroscience, 16(5), 1894–1903. https://doi.org/10.1523/JNEUROSCI.16-05-01894.1996

Halgren, E., Stapleton, J., Domalski, P., Swartz, B. E., Delgado-Escueta, A. V., Walsh, G. O., Mandelkern, M., Blahd, W., & Ropchan, J. (1991). Memory dysfunction in epilepsy patients as a derangement of normal physiology. Advances in neurology, 55, 385–410.

Helmstaedter C. (2002). Effects of chronic epilepsy on declarative memory systems. Progress in brain research, 135, 439–453. https://doi.org/10.1016/S0079-6123(02)35041-6

Hill, D. R., & Bowery, N. G. (1981). 3H-baclofen and 3H-GABA bind to bicuculline-insensitive GABA B sites in rat brain. Nature, 290(5802), 149–152. https://doi.org/10.1038/290149a0

Hill, D. R., Bowery, N. G., & Hudson, A. L. (1984). Inhibition of GABAB receptor binding by guanyl nucleotides. *Journal of neurochemistry*, *42*(3), 652–657. https://doi.org/10.1111/j.1471-4159.1984.tb02732.x

Hill D. R. (1985). GABAB receptor modulation of adenylate cyclase activity in rat brain slices. *British journal of pharmacology*, *84*(1), 249–257.

Hillman, R., Sinani, J., & Pendleton, R. (2012). The role of the GABA(B) receptor and calcium channels in a Drosophila model of Parkinson's Disease. *Neuroscience letters*, *516*(2), 167–170. https://doi.org/10.1016/j.neulet.2012.03.034

Hirsch, J. C., & Burnod, Y. (1987). A synaptically evoked late hyperpolarization in the rat dorsolateral geniculate neurons in vitro. *Neuroscience*, *23*(2), 457–468. https://doi.org/10.1016/0306-4522(87)90069-8

Houser C. R. (1990). Granule cell dispersion in the dentate gyrus of humans with temporal lobe epilepsy. Brain research, 535(2), 195–204. https://doi.org/10.1016/0006-8993(90)91601-c

Huston, E., Scott, R. H., & Dolphin, A. C. (1990). A comparison of the effect of calcium channel ligands and GABAB agonists and antagonists on transmitter release and somatic calcium channel currents in cultured neurons. *Neuroscience*, *38*(3), 721–729. https://doi.org/10.1016/0306-4522(90)90065-c

Isokawa, M., Avanzini, G., Finch, D. M., Babb, T. L., & Levesque, M. F. (1991). Physiologic properties of human dentate granule cells in slices prepared from epileptic patients. Epilepsy research, 9(3), 242–250. https://doi.org/10.1016/0920-1211(91)90058-n

Isomoto, S., Kaibara, M., Sakurai-Yamashita, Y., Nagayama, Y., Uezono, Y., Yano, K., & Taniyama, K. (1998). Cloning and tissue distribution of novel splice variants of the rat GABAB receptor. Biochemical and biophysical research communications, 253(1), 10–15. https://doi.org/10.1006/bbrc.1998.9706

Iwakiri, M., Mizukami, K., Ikonomovic, M. D., Ishikawa, M., Hidaka, S., Abrahamson, E. E., DeKosky, S. T., & Asada, T. (2005). Changes in hippocampal GABABR1 subunit expression in Alzheimer's

patients: association with Braak staging. Acta neuropathologica, 109(5), 467–474. https://doi.org/10.1007/s00401-005-0985-9

Jones, K.A., Borowsky, B., Tamm, J.A., Craig, D.A., Durkin, M.M., Dau, M., Yao, W.Y., Johnson, M., Gunwaldsen, C., Huang, L.Y., Tang, C., Shen, Q., Salon, J.A., Morse, K., Laz, T., Smith, K.E., Nagarathnam, D., Noble, S.A., Branchek, T.A., and Gerald, C. (1998). GABAB receptors functional a heterodimeric assembly of the subunits GABABR1 and GABABR2. Nature 396, 674-678. doi:10.1038/25348

Johnston, T., & Duty, S. (2003). Changes in GABA(B) receptor mRNA expression in the rodent basal ganglia and thalamus following lesion of the nigrostriatal pathway. Neuroscience, 120(4), 1027–1035. https://doi.org/10.1016/s0306-4522(03)00418-4

Kantrowitz, J. T., Francis, N. N., Salah, A., & Perkins, K. L. (2005). Synaptic depolarizing GABA Response in adults is excitatory and proconvulsive when GABAB receptors are blocked. Journal of neurophysiology, 93(5), 2656–2667. https://doi.org/10.1152/jn.01026.2004

Karbon, E. W., & Enna, S. J. (1985). Characterization of the relationship between gamma-aminobutyric acid B agonists and transmitter-coupled cyclic nucleotide-generating systems in rat brain. *Molecular pharmacology*, *27*(1), 53–59.

Karlsson, G., & Olpe, H. R. (1989). Late inhibitory postsynaptic potentials in rat prefrontal cortex may be mediated by GABAB receptors. *Experientia*, *45*(2), 157–158. https://doi.org/10.1007/BF01954857

Knight, A. R., & Bowery, N. G. (1996). The pharmacology of adenylyl cyclase modulation by GABAB receptors in rat brain slices. *Neuropharmacology*, *35*(6), 703–712. https://doi.org/10.1016/0028-3908(96)84642-9

Kaupmann, K., Huggel, K., Heid, J., Flor, P. J., Bischoff, S., Mickel, S. J., McMaster, G., Angst, C., Bittiger, H., Froestl, W., & Bettler, B. (1997). Expression cloning of GABA(B) receptors uncovers similarity to metabotropic glutamate receptors. Nature, 386(6622), 239–246. https://doi.org/10.1038/386239a0

Kaupmann, K., Malitschek, B., Schuler, V., Heid, J., Froestl, W., Beck, P., Mosbacher, J., Bischoff, S., Kulik, A., Shigemoto, R., Karschin, A., & Bettler, B. (1998). GABA(B)-receptor subtypes assemble into functional heteromeric complexes. Nature, 396(6712), 683–687. https://doi.org/10.1038/25360

Köhling, R., Lücke, A., Straub, H., Speckmann, E. J., Tuxhorn, I., Wolf, P., Pannek, H., & Oppel, F. (1998). Spontaneous sharp waves in human neocortical slices excised from epileptic patients. Brain: a journal of neurology, 121 (Pt 6), 1073–1087. https://doi.org/10.1093/brain/121.6.1073

Knowles, W. D., Awad, I. A., & Nayel, M. H. (1992). Differences of in vitro electrophysiology of hippocampal neurons from epileptic patients with mesiotemporal sclerosis versus structural lesions. Epilepsia, 33(4), 601–609. https://doi.org/10.1111/j.1528-1157.1992.tb02335.x

Krnjević K. (1974). Some neuroactive compounds in the substantia nigra. Advances in neurology, 5, 145–152.

Kuner, R., Köhr, G., Grünewald, S., Eisenhardt, G., Bach, A., & Kornau, H. C. (1999). Role of heteromer formation in GABAB receptor function. Science (New York, N.Y.), 283(5398), 74–77. https://doi.org/10.1126/science.283.5398.74

Lefkowitz R. J. (1992). G proteins. The subunit story thickens. *Nature*, *358*(6385), 372. https://doi.org/10.1038/358372a0

Liang, F., Hatanaka, Y., Saito, H., Yamamori, T., and Hashikawa, T. (2000). Differential expression of γ-aminobutyric acid type B receptor-1a and -1b variants in GABA and non-GABAergic neurons of the rat brain. J. Comp. Neurol. 416, 475-495.

Lopes, E. F., Roberts, B. M., Siddorn, R. E., Clements, M. A., & Cragg, S. J. (2019). Inhibition of Nigrostriatal Dopamine Release by Striatal GABAA and GABAB Receptors. The Journal of

neuroscience : the official journal of the Society for Neuroscience, 39(6), 1058–1065. https://doi.org/10.1523/JNEUROSCI.2028-18.2018

Loup, F., Picard, F., André, V. M., Kehrli, P., Yonekawa, Y., Wieser, H. G., & Fritschy, J. M. (2006). Altered expression of alpha3-containing GABAA receptors in the neocortex of patients with focal epilepsy. *Brain : a journal of neurology*, *129*(Pt 12), 3277–3289. https://doi.org/10.1093/brain/awl287

Lu, X-Y., Ghasemzade, B., and Kalivas, P.W. (1999). Regional distribution and cellular localisation of γ-aminobutyric acid subtype 1 receptor mRNA in the rat brain. J. Comp. Neurol. 407, 166-182.

Luhmann, H. J., & Prince, D. A. (1991). Postnatal maturation of the GABAergic system in rat neocortex. *Journal of neurophysiology*, *65*(2), 247–263. https://doi.org/10.1152/jn.1991.65.2.247

Lüscher, C., Jan, L. Y., Stoffel, M., Malenka, R. C., & Nicoll, R. A. (1997). G protein-coupled inwardly rectifying K+ channels (GIRKs) mediate postsynaptic but not presynaptic transmitter actions in hippocampal neurons. *Neuron*, *19*(3), 687–695. https://doi.org/10.1016/s0896-6273(00)80381-5

Mangan, P. S., Rempe, D. A., & Lothman, E. W. (1995). Changes in inhibitory neurotransmission in the CA1 region and dentate gyrus in a chronic model of temporal lobe epilepsy. Journal of neurophysiology, 74(2), 829–840. https://doi.org/10.1152/jn.1995.74.2.829

Mangan, P. S., & Lothman, E. W. (1996). Profound disturbances of pre- and postsynaptic GABAB-receptor-mediated processes in region CA1 in a chronic model of temporal lobe epilepsy. Journal of neurophysiology, 76(2), 1282–1296. https://doi.org/10.1152/jn.1996.76.2.1282

Marescaux, C., Vergnes, M., Liu, Z., Depaulis, A., & Bernasconi, R. (1992). GABAB receptor involvement in the control of genetic absence seizures in rats. Epilepsy research. Supplement, 9, 131–139.

Martín-Belmonte, A., Aguado, C., Alfaro-Ruíz, R., Moreno-Martínez, A. E., de la Ossa, L., Martínez-Hernández, J., Buisson, A., Früh, S., Bettler, B., Shigemoto, R., Fukazawa, Y., & Luján, R. (2020a). Reduction in the neuronal surface of post and presynaptic GABAB receptors in the hippocampus in a mouse model of Alzheimer's disease. Brain pathology (Zurich, Switzerland), 30(3), 554–575. https://doi.org/10.1111/bpa.12802

Martín-Belmonte, A., Aguado, C., Alfaro-Ruíz, R., Moreno-Martínez, A. E., de la Ossa, L., Martínez-Hernández, J., Buisson, A., Shigemoto, R., Fukazawa, Y., & Luján, R. (2020b). Density of GABAB Receptors Is Reduced in Granule Cells of the Hippocampus in a Mouse Model of Alzheimer's Disease. International journal of molecular sciences, 21(7), 2459. https://doi.org/10.3390/ijms21072459

Mathern, G. W., Mendoza, D., Lozada, A., Pretorius, J. K., Dehnes, Y., Danbolt, N. C., Nelson, N., Leite, J. P., Chimelli, L., Born, D. E., Sakamoto, A. C., Assirati, J. A., Fried, I., Peacock, W. J., Ojemann, G. A., & Adelson, P. D. (1999). Hippocampal GABA and glutamate transporter immunoreactivity in patients with temporal lobe epilepsy. Neurology, 52(3), 453–472. https://doi.org/10.1212/wnl.52.3.453

Maureille A, Fenouil T, Joubert B, et al. Isolated seizures are a common early feature of paraneoplastic anti-$GABA_B$ receptor encephalitis. *J Neurol*. 2019;266(1):195–206. doi:10.1007/s00415-018-9132-0

Mayordomo-Cava, J., Yajeya, J., Navarro-López, J. D., & Jiménez-Díaz, L. (2015). Amyloid-β(25-35) Modulates the Expression of GIRK and KCNQ Channel Genes in the Hippocampus. PloS one, 10(7), e0134385. https://doi.org/10.1371/journal.pone.0134385

Mazzuferi, M., Palma, E., Martinello, K., Maiolino, F., Roseti, C., Fucile, S., Fabene, P. F., Schio, F., Pellitteri, M., Sperk, G., Miledi, R., Eusebi, F., & Simonato, M. (2010). Enhancement of GABA(A)-current run-down in the hippocampus occurs at the first spontaneous seizure in a model of temporal lobe epilepsy. Proceedings of the National Academy of Sciences of the United States of America, 107(7), 3180–3185. https://doi.org/10.1073/pnas.0914710107

McGregor, M. M., & Nelson, A. B. (2019). Circuit Mechanisms of Parkinson's Disease. Neuron, 101(6), 1042–1056. https://doi.org/10.1016/j.neuron.2019.03.004

Meeren, H. K., van Luijtelaar, E. L., Lopes da Silva, F. H., Berdiev, R. K., Chepurnova, N. E., Chepurnov, S. A., & Coenen, A. M. (2004). Kortikotalamicheskaia teoriia proiskhozhdeniia generalizovannykh pik-volnovykh razriadov [The cortico-thalamic theory for generalised spike-wave discharges]. Uspekhi fiziologicheskikh nauk, 35(1), 3–19.

Misgeld, U., Klee, M. R., & Zeise, M. L. (1984). Differences in baclofen-sensitivity between CA3 neurons and granule cells of the guinea pig hippocampus in vitro. *Neuroscience letters*, *47*(3), 307–311. https://doi.org/10.1016/0304-3940(84)90531-7

Moser A, Hanssen H, Wandinger KP. Excessively increased CSF glutamate levels in $GABA_B$-receptor antibody associated encephalitis: A case report. *J Neurol Sci*. 2018;388:10–11. doi:10.1016/j.jns.2018.02.041

Mott, D. D., & Lewis, D. V. (1994). The pharmacology and function of central GABAB receptors. International review of neurobiology, 36, 97–223. https://doi.org/10.1016/s0074-7742(08)60304-9

Muñoz, A., Huntsman, M. M., & Jones, E. G. (1998). GABA(B) receptor gene expression in monkey thalamus. The Journal of comparative neurology, 394(1), 118–126. https://doi.org/10.1002/(sici)1096-9861(19980427)394:1<118::aid-cne9>3.0.co;2-3

Nava-Mesa, M. O., Jiménez-Díaz, L., Yajeya, J., & Navarro-Lopez, J. D. (2013). Amyloid-β induces synaptic dysfunction through G protein-gated inwardly rectifying potassium channels in the fimbria-CA3 hippocampal synapse. Frontiers in cellular neuroscience, 7, 117. https://doi.org/10.3389/fncel.2013.00117

Ng, G.Y.K., Clark, J., Coulombe, N., Ethier, N., Herbert, T.E., Sullivan, R., Kargman, S., Chateauneuf, A., Tsukamoto, N., Mezey, E., Johnson, M.P., Liu, Q., Kolakowski, L.F. Jr, Evans, J.F., Bonner, T.I., and O'Neill, G.P. (1999). Identification of a GABAB receptor subunit, gB2, required for functional GABAB receptor activity. J. Biol. Chem. 274, 7607-7610. doi:10.1074/jbc.274.12.7607

Niddam, R., Dubois, A., Scatton, B., Arbilla, S., & Langer, S. Z. (1987). Autoradiographic localization of [3H]zolpidem binding sites in the rat CNS: comparison with the distribution of [3H]flunitrazepam binding sites. *Journal of neurochemistry*, *49*(3), 890–899. https://doi.org/10.1111/j.1471-4159.1987.tb00977.

Nishimura, T., Schwarzer, C., Gasser, E., Kato, N., Vezzani, A., & Sperk, G. (2005). Altered expression of GABA(A) and GABA(B) receptor subunit mRNAs in the hippocampus after kindling and electrically induced status epilepticus. Neuroscience, 134(2), 691–704. https://doi.org/10.1016/j.neuroscience.2005.04.013

Odagaki, Y., Nishi, N., & Koyama, T. (2000). Functional coupling of GABA(B) receptors with G proteins that are sensitive to N-ethylmaleimide treatment, suramin, and benzalkonium chloride in rat cerebral cortical membranes. *Journal of neural transmission (Vienna, Austria : 1996)*, *107*(10), 1101–1116. https://doi.org/10.1007/s007020070024

Odagaki, Y., & Koyama, T. (2001). Identification of galpha subtype(s) involved in gamma-aminobutyric acid(B) receptor-mediated high-affinity guanosine triphosphatase activity in rat cerebral cortical membranes. *Neuroscience letters*, *297*(2), 137–141. https://doi.org/10.1016/s0304-3940(00)01692-x

Olpe, H. R., Steinmann, M. W., Ferrat, T., Pozza, M. F., Greiner, K., Brugger, F., Froestl, W., Mickel, S. J., & Bittiger, H. (1993). The actions of orally active GABAB receptor antagonists on GABAergic transmission in vivo and in vitro. European journal of pharmacology, 233(2-3), 179–186. https://doi.org/10.1016/0014-2999(93)90048-m

Paris-Robidas S, Brochu E, Sintes M, et al. Defective dentate nucleus GABA receptors in essential tremor. *Brain*. 2012;135(Pt 1):105–116. doi:10.1093/brain/awr301

Pfrieger, F. W., Gottmann, K., & Lux, H. D. (1994). Kinetics of GABAB receptor-mediated inhibition of calcium currents and excitatory synaptic transmission in hippocampal neurons in vitro. *Neuron*, *12*(1), 97–107. https://doi.org/10.1016/0896-6273(94)90155-4

Pilipenko, V., Narbute, K., Beitnere, U., Rumaks, J., Pupure, J., Jansone, B., & Klusa, V. (2018). Very low doses of muscimol and baclofen ameliorate cognitive deficits and regulate protein expression in the brain of a rat model of streptozocin-induced Alzheimer's disease. European journal of pharmacology, 818, 381–399. https://doi.org/10.1016/j.ejphar.2017.11.012

Pirker, S., Schwarzer, C., Czech, T., Baumgartner, C., Pockberger, H., Maier, H., Hauer, B., Sieghart, W., Furtinger, S., & Sperk, G. (2003). Increased expression of GABA(A) receptor beta-subunits in the hippocampus of patients with temporal lobe epilepsy. Journal of neuropathology and experimental neurology, 62(8), 820–834. https://doi.org/10.1093/jnen/62.8.820

Princivalle, A. P., Pangalos, M. N., Bowery, N. G., & Spreafico, R. (2001). Distribution of GABA(B(1a)), GABA(B(1b)) and GABA(B2) receptor protein in cerebral cortex and thalamus of adult rats. Neuroreport, 12(3), 591–595. https://doi.org/10.1097/00001756-200103050-00032

Princivalle, A. P., Duncan, J. S., Thom, M., & Bowery, N. G. (2002). Studies of GABA(B) receptors labelled with [(3)H]-CGP62349 in hippocampus resected from patients with temporal lobe epilepsy. British journal of pharmacology, 136(8), 1099–1106. https://doi.org/10.1038/sj.bjp.0704812

Princivalle, A. P., Duncan, J. S., Thom, M., & Bowery, N. G. (2003). GABA(B1a), GABA(B1b) AND GABA(B2) mRNA variants expression in hippocampus resected from patients with temporal lobe epilepsy. Neuroscience, 122(4), 975–984. https://doi.org/10.1016/j.neuroscience.2003.08.044

Rainnie, D. G., Asprodini, E. K., & Shinnick-Gallagher, P. (1991). Inhibitory transmission in the basolateral amygdala. *Journal of neurophysiology*, *66*(3), 999–1009. https://doi.org/10.1152/jn.1991.66.3.999

Rascol, O., Dutar, P., & Lamour, Y. (1989). Involvement of a pertussis toxin-sensitive G-protein in the pharmacological properties of septo-hippocampal neurones. *British journal of pharmacology*, *96*(4), 956–960. https://doi.org/10.1111/j.1476-5381.1989.tb11907.x

Rekik, L., Daguin-Nerrière, V., Petit, J. Y., & Brachet, P. (2011). γ-Aminobutyric acid type B receptor changes in the rat striatum and substantia nigra following intrastriatal quinolinic acid lesions. Journal of neuroscience research, 89(4), 524–535. https://doi.org/10.1002/jnr.22574

Rocha, L., Alonso-Vanegas, M., Martínez-Juárez, I. E., Orozco-Suárez, S., Escalante-Santiago, D., Feria-Romero, I. A., Zavala-Tecuapetla, C., Cisneros-Franco, J. M., Buentello-García, R. M., & Cienfuegos, J. (2015). GABAergic alterations in neocortex of patients with pharmacoresistant temporal lobe epilepsy can explain the comorbidity of anxiety and depression: the potential impact of clinical factors. Frontiers in cellular neuroscience, 8, 442. https://doi.org/10.3389/fncel.2014.00442

Rosas-Arellano A, Estrada-Mondragón A, Mantellero CA, Tejeda-Guzmán C, Castro MA. The adjustment of γ-aminobutyric acid$_A$ tonic subunits in Huntington's disease: from transcription to translation to synaptic levels into the neostriatum. *Neural Regen Res*. 2018;13(4):584–590. doi:10.4103/1673-5374.230270

Ruano, D., Vizuete, M., Cano, J., Machado, A., & Vitorica, J. (1992). Heterogeneity in the allosteric interaction between the gamma-aminobutyric acid (GABA) binding site and three different benzodiazepine binding sites of the GABAA/benzodiazepine receptor complex in the rat nervous system. *Journal of neurochemistry*, *58*(2), 485–493. https://doi.org/10.1111/j.1471-4159.1992.tb09747.x

Saint, D. A., Thomas, T., & Gage, P. W. (1990). GABAB agonists modulate a transient potassium current in cultured mammalian hippocampal neurons. *Neuroscience letters*, *118*(1), 9–13. https://doi.org/10.1016/0304-3940(90)90236-3

Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58(4):512–521. doi:10.1111/epi.13709

Schijns, O., Karaca, Ü., Andrade, P., de Nijs, L., Küsters, B., Peeters, A., Dings, J., Pannek, H., Ebner, A., Rijkers, K., & Hoogland, G. (2015). Hippocampal GABA transporter distribution in patients with temporal lobe epilepsy and hippocampal sclerosis. Journal of chemical neuroanatomy, 68, 39–44. https://doi.org/10.1016/j.jchemneu.2015.07.004

Schofield, P. R., Darlison, M. G., Fujita, N., Burt, D. R., Stephenson, F. A., Rodriguez, H., Rhee, L. M., Ramachandran, J., Reale, V., & Glencorse, T. A. (1987). Sequence and functional expression of the GABA A receptor shows a ligand-gated receptor super-family. *Nature*, *328*(6127), 221–227. https://doi.org/10.1038/328221a0

Schreurs, B. G., Sanchez-Andres, J. V., & Alkon, D. L. (1992). GABA-induced responses in Purkinje cell dendrites of the rabbit cerebellar slice. *Brain research*, *597*(1), 99–107. https://doi.org/10.1016/0006-8993(92)91510-l

Schumacher H, Meyer T, Prüss H. $GABA_B$ receptor encephalitis in a patient diagnosed with amyotrophic lateral sclerosis. *BMC Neurol*. 2019;19(1):41. Published 2019 Mar 14. doi:10.1186/s12883-019-1269-7

Scott, R. H., Pearson, H. A., & Dolphin, A. C. (1991). Aspects of vertebrate neuronal voltage-activated calcium currents and their regulation. *Progress in neurobiology*, *36*(6), 485–520. https://doi.org/10.1016/0301-0082(91)90014-r

Seifert, G., Carmignoto, G., & Steinhäuser, C. (2010). Astrocyte dysfunction in epilepsy. Brain research reviews, 63(1-2), 212–221. https://doi.org/10.1016/j.brainresrev.2009.10.004

Sheilabi, M. A., Battacharyya, D., Caetano, L., Thom, M., Reuber, M., Duncan, J. S., & Princivalle, A. P. (2018). Quantitative expression and localization of GABAB receptor protein subunits in hippocampi from patients with refractory temporal lobe epilepsy. Neuropharmacology, 136(Pt A), 117–128. https://doi.org/10.1016/j.neuropharm.2017.08.001

Shorvon S. D. (2011). The causes of epilepsy: changing concepts of etiology of epilepsy over the past 150 years. Epilepsia, 52(6), 1033–1044. https://doi.org/10.1111/j.1528-1167.2011.03051.x

Sieghart, W., Eichinger, A., Richards, J. G., & Möhler, H. (1987). Photoaffinity labeling of benzodiazepine receptor proteins with the partial inverse agonist [3H]Ro 15-4513: a biochemical and autoradiographic study. *Journal of neurochemistry*, *48*(1), 46–52. https://doi.org/10.1111/j.1471-4159.1987.tb13125.x

Sloviter R. S. (1994). The functional organization of the hippocampal dentate gyrus and its relevance to the pathogenesis of temporal lobe epilepsy. Annals of neurology, 35(6), 640–654. https://doi.org/10.1002/ana.410350604

Smith, G. B., & Olsen, R. W. (1995). Functional domains of GABAA receptors. *Trends in pharmacological sciences*, *16*(5), 162–168. https://doi.org/10.1016/s0165-6147(00)89009-4

Smith, Y., Charara, A., Hanson, J. E., Paquet, M., & Levey, A. I. (2000). GABA(B) and group I metabotropic glutamate receptors in the striatopallidal complex in primates. Journal of anatomy, 196 (Pt 4)(Pt 4), 555–576. https://doi.org/10.1046/j.1469-7580.2000.19640555.x

Sperk, G., Furtinger, S., Schwarzer, C., & Pirker, S. (2004). GABA and its receptors in epilepsy. Advances in experimental medicine and biology, 548, 92–103. https://doi.org/10.1007/978-1-4757-6376-8_7

Stafstrom, C. E., & Carmant, L. (2015). Seizures and epilepsy: an overview for neuroscientists. Cold Spring Harbor perspectives in medicine, 5(6), a022426. https://doi.org/10.1101/cshperspect.a022426

Stefani, A., Spadoni, F., Giacomini, P., Lavaroni, F., & Bernardi, G. (1999). The modulation of calcium current by GABA metabotropic receptors in a sub-population of pallidal neurons. The European journal of neuroscience, 11(11), 3995–4005. https://doi.org/10.1046/j.1460-9568.1999.00836.x

Stefanits, H., Milenkovic, I., Mahr, N., Pataraia, E., Baumgartner, C., Hainfellner, J. A., Kovacs, G. G., Kasprian, G., Sieghart, W., Yilmazer-Hanke, D., & Czech, T. (2019). Alterations in GABAA Receptor

Subunit Expression in the Amygdala and Entorhinal Cortex in Human Temporal Lobe Epilepsy. Journal of neuropathology and experimental neurology, 78(11), 1022–1048. https://doi.org/10.1093/jnen/nlz085

Stewart, L. S., Wu, Y., Eubanks, J. H., Han, H., Leschenko, Y., Perez Velazquez, J. L., Cortez, M. A., & Snead, O. C., 3rd (2009). Severity of atypical absence phenotype in GABAB transgenic mice is subunit specific. Epilepsy & behavior : E&B, 14(4), 577–581. https://doi.org/10.1016/j.yebeh.2009.01.019

Sutula, T., Cascino, G., Cavazos, J., Parada, I., & Ramirez, L. (1989). Mossy fiber synaptic reorganization in the epileptic human temporal lobe. Annals of neurology, 26(3), 321–330. https://doi.org/10.1002/ana.410260303

Sutula, T. P., & Hermann, B. (1999). Progression in mesial temporal lobe epilepsy. Annals of neurology, 45(5), 553–556.

Takahashi, T., Kajikawa, Y., & Tsujimoto, T. (1998). G-Protein-coupled modulation of presynaptic calcium currents and transmitter release by a GABAB receptor. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *18*(9), 3138–3146. https://doi.org/10.1523/JNEUROSCI.18-09-03138.1998

Tang BL. Amyloid Precursor Protein (APP) and GABAergic Neurotransmission. *Cells*. 2019;8(6):550. Published 2019 Jun 6. doi:10.3390/cells8060550

Teichgräber, L. A., Lehmann, T. N., Meencke, H. J., Weiss, T., Nitsch, R., & Deisz, R. A. (2009). Impaired function of GABA(B) receptors in tissues from pharmacoresistant epilepsy patients. Epilepsia, 50(7), 1697–1716. https://doi.org/10.1111/j.1528-1167.2009.02094.

Thomas, P. M., Phillips, J. P., Delanty, N., & O'Connor, W. T. (2003). Elevated extracellular levels of glutamate, aspartate and gamma-aminobutyric acid within the intraoperative, spontaneously epileptiform human hippocampus. Epilepsy research, 54(1), 73–79. https://doi.org/10.1016/s0920-1211(03)00035-4

Thomas, P. M., Phillips, J. P., & O'Connor, W. T. (2005). Microdialysis of the lateral and medial temporal lobe during temporal lobe epilepsy surgery. Surgical neurology, 63(1), 70–79. https://doi.org/10.1016/j.surneu.2004.02.031

Thompson, S. M., & Gähwiler, B. H. (1992). Effects of the GABA uptake inhibitor tiagabine on inhibitory synaptic potentials in rat hippocampal slice cultures. *Journal of neurophysiology*, *67*(6), 1698–1701. https://doi.org/10.1152/jn.1992.67.6.1698

Tyagi, R. K., Bisht, R., Pant, J., Kumar, P., Majeed, A. B., & Prakash, A. (2015). Possible role of GABA-B receptor modulation in MPTP induced Parkinson's disease in rats. Experimental and toxicologic pathology: official journal of the Gesellschaft fur Toxikologische Pathologie, 67(2), 211–217. https://doi.org/10.1016/j.etp.2014.12.001

Tysnes, O. B., & Storstein, A. (2017). Epidemiology of Parkinson's disease. Journal of neural transmission (Vienna, Austria : 1996), 124(8), 901–905. https://doi.org/10.1007/s00702-017-1686-y

Van Paesschen, W., Revesz, T., Duncan, J. S., King, M. D., & Connelly, A. (1997). Quantitative neuropathology and quantitative magnetic resonance imaging of the hippocampus in temporal lobe epilepsy. Annals of neurology, 42(5), 756–766. https://doi.org/10.1002/ana.410420512

Vigot, R., & Batini, C. (1997). GABA(B) receptor activation of Purkinje cells in cerebellar slices. *Neuroscience research*, *29*(2), 151–160. https://doi.org/10.1016/s0168-0102(97)00087-4

Williams, S., & Lacaille, J. C. (1992). GABAB receptor-mediated inhibitory postsynaptic potentials evoked by electrical stimulation and by glutamate stimulation of interneurons in stratum lacunosum-moleculare in hippocampal CA1 pyramidal cells in vitro. *Synapse (New York, N.Y.)*, *11*(3), 249–258. https://doi.org/10.1002/syn.890110309

Winblad B, Amouyel P, Andrieu S, Ballard C, Brayne C, Brodaty H, Cedazo-Minguez A, Dubois B, Edvardsson D, Feldman H, Fratiglioni L, Frisoni GB, Gauthier S, Georges J, Graff C, Iqbal K, Jessen F, Johansson G, Jönsson L, Kivipelto M, Knapp M, Mangialasche F, Melis R, Nordberg A, Rikkert MO, Qiu C, Sakmar TP, Scheltens P, Schneider LS, Sperling R, Tjernberg LO, Waldemar G, Wimo A, Zetterberg H. Defeating Alzheimer's disease and other dementias: a priority for European science and society. Lancet Neurol. 2016 Apr;15(5):455-532. doi: 10.1016/S1474-4422(16)00062-4. PMID: 26987701.

Wojcik, W. J., & Neff, N. H. (1984). gamma-aminobutyric acid B receptors are negatively coupled to adenylate cyclase in brain, and in the cerebellum these receptors may be associated with granule cells. *Molecular pharmacology*, *25*(1), 24–28.

Wojcik, W. J., Travagli, R. A., Costa, E., & Bertolino, M. (1990). Baclofen inhibits with high affinity an L-type-like voltage-dependent calcium channel in cerebellar granule cell cultures. *Neuropharmacology*, *29*(10), 969–972. https://doi.org/10.1016/0028-3908(90)90150-p

Wu, C., & Leung, L. S. (1997). Partial hippocampal kindling decreases efficacy of presynaptic GABAB autoreceptors in CA1. The Journal of neuroscience : the official journal of the Society for Neuroscience, 17(23), 9261–9269. https://doi.org/10.1523/JNEUROSCI.17-23-09261.1997

Yu, Z., Cheng, G., & Hu, B. (1997). Mechanism of colchicine impairment on learning and memory, and protective effect of CGP36742 in mice. Brain research, 750(1-2), 53–58. https://doi.org/10.1016/s0006-8993(96)01158-4

Zentner, J., Hufnagel, A., Wolf, H. K., Ostertun, B., Behrens, E., Campos, M. G., Solymosi, L., Elger, C. E., Wiestler, O. D., & Schramm, J. (1995). Surgical treatment of temporal lobe epilepsy: clinical, radiological, and histopathological findings in 178 patients. Journal of neurology, neurosurgery, and psychiatry, 58(6), 666–673. https://doi.org/10.1136/jnnp.58.6.666