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Implication for treatment: $GABA_A$ receptors in aging, Down syndrome and Alzheimer's disease

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Abstract

In addition to progressive dementia, Alzheimer's disease (AD) is characterized by increased incidence of seizure activity. Although originally discounted as a secondary process occurring as a result of neurodegeneration, more recent data suggest that alterations in excitatory-inhibitory (E/I) balance occur in AD and may be a primary mechanism contributing AD cognitive decline. In this study, we discuss relevant research and reports on the $GABA_A$ receptor in developmental disorders, such as Down syndrome, in healthy aging, and highlight documented aberrations in the GABAergic system in AD. Stressing the importance of understanding the subunit composition of individual $GABA_A$ receptors, investigations demonstrate alterations of particular $GABA_A$ receptor subunits in AD, but overall sparing of the GABAergic system. In this study, we review experimental data on the GABAergic system in the pathobiology of AD and discuss relevant therapeutic implications. When developing AD therapeutics that modulate GABA it is important to consider how E/I balance impacts AD pathogenesis and the relationship between seizure activity and cognitive decline.

Keywords

age; Alzheimer's disease; Down syndrome; $GABA_A$; GABA receptor; seizure

Relevance of E/I balance to DS and AD neuropathology

Alzheimer's disease (AD) is definitively diagnosed postmortem by the appearance of extracellular β-amyloid (Aβ) plaques and intracellular neurofibrillary tangles. The AD brain is also characterized by extensive neuronal and synaptic loss in areas of the brain essential for cognitive and memory functions, such as the cerebral cortex and hippocampus. Approximately 90% of hippocampal neurons confer excitatory glutamatergic neurotransmission; the remaining 10% of hippocampal neurons are inhibitory in nature, of which the majority is GABAergic. A long-standing hypothesis in the AD field suggests that increasing oxidative or metabolic stress can lead to excessive glutamatergic tone, which is thought to lead neuronal loss in AD. Considerable research has focused on the role of calcium-permeable glutamate receptors in promoting glutamate-mediated excitotoxicity in AD. An over-stimulation of NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors by glutamate has been demonstrated to induce cell death by calcium-dependent pathways (Pellegrini-Giampietro *et al*. 1997; Arundine and Tymianski 2004). In line with this hypothesis, many studies of the AD brain have found reductions both in glutamate-releasing cells (Hyman *et al*. 1984) and in glutamate receptor subunits

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(Ikonomovic *et al*. 1999, 2000; Carter *et al*. 2004; Mishizen-Eberz *et al*. 2004), reviewed in (Mishizen *et al*. 2000; Armstrong *et al*. 2003). Accepting that stimulation of ionotropic glutamate receptors contribute to the pathogenesis of AD, and the view that this could serve to disrupt E/I balance, it is important to also consider that disruptions or alterations in GABA neurotransmission or inhibitory $GABA_A$ receptors may significantly impact hippocampal structure and function. Even sparing of the GABAergic system in the face of severe glutamatergic loss can be envisioned to cause disregulation of E/I balance. Interestingly, both Down syndrome (DS) and AD are characterized by increased seizure activity (Menendez 2005; Palop and Mucke 2009a,b; Abou-Khalil 2010; De Simone *et al*. 2010), which not only suggests a disruption of E/I balance, but begs the question of which neurotransmitter systems are responsible. We will discuss evidence that the E/I balance is abnormal in these diseases and that this abnormality can play a causative role in the increased seizure activity observed and in the pathogenesis and cognitive disruption in AD and DS. We will argue that changes in E/I balance mark these disorders and serve to motivate studies to more clearly define the causes and consequences of disruption in circuits.

GABAergic receptor system

GABA is the primary inhibitory neurotransmitter in the mammalian brain. The inhibitory actions of GABA are mediated by three receptor classes ($GABA_A$, $GABA_B$ and $GABA_C$/$GABA_{A\text{-}\rho}$). The ligand-gated $GABA_A$ receptor regulates the majority of fast inhibitory neurotransmission in the vertebrate brain. Conversely, slow inhibitory responses are mediated by $GABA_B$ receptors. $GABA_B$ receptors are present both pre- and post-synaptically and are transmembrane receptors linked to G-proteins coupled to adenylyl cyclase, voltage-gated calcium channels, and inwardly directed potassium channels. They exist in two forms (B1 and B2) as heterodimers in neuronal membranes (Bowery *et al*. 1980, 2002). $GABA_B$ receptors are modulated by analogues of GABA. A third type of GABA receptor, the $GABA_{A\text{-}\rho}$ receptor, was originally designated a distinct subtype, $GABA_C$. These ligand-gated receptors mediate slow and more sustained responses and are primarily expressed in retinal bipolar and horizontal cells (Sivilotti and Nistri 1991; Johnston *et al*. 2003). Pharmacologically, $GABA_{A\text{-}\rho}$ receptors are not modulated by traditional $GABA_A$ receptor modulators (e.g. benzodiazepines, barbiturates and neuroactive steroids) or even GABA itself (Johnston *et al*. 2003). Because $GABA_{A\text{-}\rho}$ receptors are exclusively composed of the ρ subunit of the $GABA_A$ receptor, the International Union of Basic and Clinical Pharmacology now recommends that `$GABA_C$' no longer be used (Olsen and Sieghart 2008).

$GABA_A$ receptor structure in the CNS

Because of its diverse role in the CNS and implications in epilepsy, drug responses and in disease states, this review will focus exclusively on the $GABA_A$ receptor. The $GABA_A$ receptor contains an intrinsic ligand-gated Cl^- channel, formed by the pentameric assembly of many types of subunits. At least 20 genes encoding distinct receptor subunits have been identified; they are grouped according to their degree of sequence identity (α1–6, β1–4, γ1–3, ρ1–3, δ, ε, π and θ subunits) (Olsen *et al*. 1990; Macdonald and Olsen 1994; Rabow *et al*. 1995; Mohler *et al*. 1996; Barnard *et al*. 1998; Bonnert *et al*. 1999; Whiting *et al*. 1999). Subunit composition intrinsic to a particular $GABA_A$ receptor may be heterogeneous, although the majority comprised two α and two β subunits and one γ subunit (Li and De Blas 1997; Jechlinger *et al*. 1998; Farrar *et al*. 1999). Alternatively, some $GABA_A$ receptors have been reported to contain 2α, 1β and 2γ (Backus *et al*. 1993; Gutierrez *et al*. 1994; Khan *et al*. 1996a,b). A variety of anatomical studies have demonstrated that the α1, α2, α5, β2, β3, and γ2 subunits are widely expressed in the rodent and human hippocampus (De Blas *et*

al. 1988; Houser *et al*. 1988; Olsen *et al*. 1990; Wisden and Seeburg 1992; Moreno *et al*. 1994; Fritschy and Mohler 1995; Miralles *et al*. 1999; Pirker *et al*. 2000).

Using genetic, molecular and pharmacological tools, one can point to the following activities of distinct types of receptors, as judged by their mediation of benzodiazepine activities. Receptors containing the α1, β2/3 and γ2 subunits mediate sedative, anterograde amnestic and anticonvulsant actions, whereas receptors containing subunits α2, β2/3, and γ2 mediate anxiolytic and muscle relaxation (Olsen and Sieghart 2009). Receptors containing α1, β2, and γ2 subunits are the most abundant subtype of the $GABA_A$ receptor in the brain and comprises the major benzodiazepine binding site (Olsen and Sieghart 2009). Pharmacological studies indicate that α5 subunit is very abundant in hippocampus and is a key subunit involved in learning and memory (Collinson *et al*. 2002; Dawson *et al*. 2006; Ballard *et al*. 2009). It is found within receptors containing the recombinant structure β2/3 and γ2 subunits (Sur *et al*. 1998; Howell *et al*. 2000). This receptor complex is highly sensitive to GABA, and generates tonic inhibition and transient inhibitory potentials (Klausberger 2009). Expression is unique compared to other receptors as α5 containing receptors are located both synaptically and perisynaptically on dendrites. Twenty-five per cent of all receptors in hippocampus are α5-containing (Klausberger 2009; Olsen and Sieghart 2009). In the hippocampal formation, abundance is particularly high in the CA1 and CA3 regions and in subiculum. Abundance is also high in inner layers of cortex and in olfactory bulb (Olsen and Sieghart 2009).

The locus for modulating the intrinsic Cl^- channel of $GABA_A$ receptors is through the binding of specific chemicals to individual subunits. Mouse models have been very useful for deciphering the behavioral and cognitive contributions of individual $GABA_A$ receptor subunits. As mentioned above, they suggest that anxiolytic, myorelaxant and sedative effect of benzodiazepines are mediated primarily through receptors containing the α and γ family of subunits (Whiting 2003; Steiger and Russek 2004; Rudolph and Mohler 2006). Other drugs, such as alcohols, steroids, and certain anesthetics have been found to act primarily via receptors containing the β family of subunits. Increased affinity of $GABA_A$ receptors to benzodiazepines may be explained by the presence of a1 in the $GABA_A$ receptor complex, whereas lower affinity receptors appear to be composed of α2, α3, α5 subunits (Ruano *et al*. 1991, 1995). These latter data, in particular, indicate that increases or decreases in the proportion of receptors containing a particular α subunit may likely reflect the affinity of the receptor for the specific class of benzodiazepine.

Biology of excitatory and inhibitory systems in aging and AD

Changes in the aging brain

Studies using radioligand-binding studies demonstrate few age-related changes in the overall number, total binding or affinity of $GABA_A$ receptors (Heusner and Bosmann 1981; Pedigo *et al*. 1981; Tsang *et al*. 1982; Komiskey and MacFarlan 1983; Reeves and Schweizer 1983; Komiskey 1987; Meyer *et al*. 1995). Likewise, no age-related alterations in total $GABA_A$ receptor binding, agonist affinity or in hippocampal inhibitory synaptic potentials been observed in the aged rodent hippocampus (Wenk *et al*. 1991; Ruano *et al*. 1992). In contrast, microarray and quantitative PCR studies of human and non-human primates have found many age-related changes (both increases and decreases) in mRNA of specific α, β and γ subunits in frontal cortex (Hashimoto *et al*. 2008; Fillman *et al*. 2009; Duncan *et al*. 2010). Furthermore, studies examining ion flux in membrane vesicles have revealed functional changes in $GABA_A$ receptor during aging (Concas *et al*. 1988; Erdo *et al*. 1989; Mhatre and Ticku 1992; Shaw and Scarth 1992; Ruano *et al*. 1995). Focusing on the expression of specific subunits, age-related increases α_1 binding sites has been reported in the hippocampus, with the greatest increases in binding density in the dentate gyrus (Ruano *et*

al. 1995). Corresponding increases in α1-containing $GABA_A$ receptors have also been found (Gutierrez *et al*. 1996b). Supporting the view that increased GABAergic signaling efficiency does occur during aging, and may be subregion-specific, decreased GABA levels have been reported in the medial septum of aged rats (Banay-Schwartz *et al*. 1989) without an age-related impairment of inhibitory synaptic transmission reported in the lateral septum (Garcia and Jaffard 1993). Using acutely dissociated neurons from the medial septum, age-related alterations in $GABA_A$ receptor pharmacological profile have been found; midazolam, which is known to bind to α subunit containing $GABA_A$ receptors, was found to produce a greater potentiation of GABA-mediated currents in aged cells (Griffith and Murchison 1995). These data are consistent with the body of work suggesting enhanced benzodiazepine activity with age. Although incomplete, existing data point to age-related changes in receptor subunit composition that can be envisioned to modify ligand binding, channel kinetics, and/or ion specificity. Whether these changes can impact cognitive function has yet to be determined.

Because the individual subunits of the $GABA_A$ receptor can differently modulate channel function, studies directed at examining their contribution to $GABA_A$ receptor function have been useful for defining age-related changes. From these data, it is seems possible and even likely that altered drug responses seen with aging may be related to changes in the molecular composition of the $GABA_A$ receptor. Although temping to interpret these changes as impacting receptor pharmacology, it is important to consider that these changes may impact local networks that control E/I balance. Changes in this balance may lead to seizure activity or render neurons more vulnerable to insults or disease.

Anatomical and biochemical approaches to age-related changes in the $GABA_A$ receptor have also yielded somewhat inconsistent data. These studies have the ability to document specific changes in particular subunits and afford a greater understanding of specific molecular composition of $GABA_A$ receptors. *In situ* hybridization studies directed against individual subunits have demonstrated age-related decreases in β2, β3, γ2S, γ2L, and α1 mRNA in the rat inferior colliculus (Gutierrez *et al.* 1994). Likewise, age-related decreases in γ2S and γ2L mRNA were observed in the cerebellum of rat. In contrast, in the cortex γ2S showed no age-related changes whereas γ2L displayed a significant reduction (Gutierrez *et al.* 1996a). In the hippocampus, α1 mRNA levels have been reported to be significantly increased in aged rats, with the dentate gyrus displaying the largest increases. No significant changes were observed in the expression of β2, β3 and γ2 subunits (Gutierrez *et al.* 1996a; b). Age-related increases in α1 mRNA have also been reported in the rat cortex but not in the cerebellum (Mhatre and Ticku 1992) in which an age-related increase in α6 mRNA was found. This study concluded that underlying these various findings might be a selective modulation in the stoichiometry of the $GABA_A$ receptor in aging. A report by (Ruano *et al.* 2000) also demonstrated marked increases in α1 mRNA in aged animals.

Biochemical studies of $GABA_A$ receptor subunits in the rat auditory system demonstrated marked increases in the γ1 subunit and decreases in the α1 subunit protein within the inferior colliculus. Additionally, when GABA-mediated chloride flux was measured, chloride flux was found significantly increased in aged animals (Caspary *et al.* 1999). Different from studies in rodents, immunohistochemical studies of the aged non-human primate have demonstrated reductions in the α1 subunit in the hippocampus; there was marked intersubject variability in aged animals was found in the β2/3 subunit (Rissman *et al.* 2006).

In interpreting the functional implications of age-related data, it is important to consider that in the adult rat brain α1, β2, and γ2 are the most abundantly expressed subunits (Ruano *et al.* 1994a,b). As we have suggested in previous commentaries, based on these data it is reasonable to consider that in the aged brain, decreases in a particular $GABA_A$ receptor subunit may be compensated with the increase expression of a substitute α,β, or γ subunit,

thereby yielding $GABA_A$ receptors with different subunit composition and different functional properties (Rissman *et al.* 2007). This view is consistent with the observed age-related changes in benzodiazepine binding properties of the $GABA_A$ receptor in the hippocampus. For example, as discussed earlier, high affinity benzodiazepine receptor pharmacology is thought to involve the presence of α1 in the $GABA_A$ receptor complex, whereas the lower affinity benzodiazepine receptors are thought to be due to the presence of α2, α3, α5 (Ruano *et al.* 1991, 1995). Therefore, an increase or decrease in the proportion of receptors containing a particular α subunit will likely be reflected in the affinity of the receptor for the specific class of benzodiazepine. Thus, in the elderly, enhanced responsiveness to benzodiazepines may be explained by changes in the composition of the $GABA_A$ receptor, rather than to emotional or physical disease, over- or malnutrition, and/or use or abuse of other medications. Of considerable importance as well is that changes in the pharmacokinetics of drug elimination in the elderly with the slower elimination of drugs that act on $GABA_A$ receptors.

Changes in the AD brain

AD is a progressive neurodegenerative disorder that leads to the loss of cognitive functions such as executive function, learning and memory. Underlying such deficits is the selective vulnerability and loss of function of specific neuronal populations within particular brain regions. For example, it is well known that basal forebrain cholinergic neurons, noradrenergic and serotoninergic neurons of the brainstem, and hippocampal glutamatergic cell populations are particularly vulnerable in AD. Modulating the dynamic balance of these excitatory systems are the inhibitory actions of GABA-mediated prominently via $GABA_A$ receptors. Interestingly, in contrast to the marked deficits seen in cholinergic and glutamatergic systems, the current literature supports the view that GABAergic neurons and receptors appear resistant to neurodegeneration. Relative preservation of the GABAergic system could be viewed as exonerating inhibitory mechanisms in AD pathogenesis, but just the opposite is suggested by understanding the important dynamic balance that must be achieved in circuits in which both excitatory and inhibitory neurotransmission are active. To examine more clearly the impact of changes in AD, investigators have examined the whether or not and to what extent there is differential vulnerability of GABAergic signaling in this disorder.

The precise mechanisms underlying selective neuronal vulnerability are currently unknown. Complicating this analysis is the difficulty in obtaining well-preserved postmortem human samples. The issues include prompt tissue collection, optimal handling and storage, and heterogeneity of changes between patients. Furthermore, with specific reference to inhibitory neurotransmission, recent work suggests that location must be more fully defined. Although predominantly viewed as post-synaptic receptors, depending on the subunit composition, $GABA_A$ receptors can also have extrasynaptic or pre-synaptic locations (Kullmann *et al.* 2005).

Despite the relative sparing of $GABA_A$ receptors in AD, it is possible that the specific subunit composition of these receptors may undergo alterations with disease progression. Several investigations have demonstrated an involvement of the GABAergic neurotransmitter system in AD (for review, see Marczynski 1995, 1998). As a whole, the current literature supports the view that GABAergic neurons and receptors appear more resistant to loss in AD, with only modest loss of GABA neurons (Rossor 1982; Mountjoy *et al.* 1984; Lowe *et al.* 1988; Reinikainen *et al.* 1988). The majority of such investigations have focused upon the hippocampus, a brain area known to be effected very early and severely in AD.

Radioligand binding studies demonstrate mild reductions in $GABA_A$/or benzodiazepine binding sites in the AD brain (Chu *et al.* 1987a,b; Vogt *et al.* 1991). Other investigations found no reduction in $GABA_A$ receptor binding in AD (Greenamyre *et al.* 1987; Jansen *et al.* 1990; Meyer *et al.* 1995). Utilizing benzodiazepine radioligands specific to the $GABA_A$ α5 subunit (Howell *et al.* 2000) found reductions in binding in the CA1, entorhinal and perirhinal cortices of AD patients.

Similar to that found for specific α5 radioligand binding, biochemical investigations utilizing western blot demonstrated moderate reductions in α5, in the hippocampus, whereas other $GABA_A$ receptor subunits investigated remained unchanged with increasing AD neuropathology (Rissman *et al.* 2003). Immunohistochemical investigations demonstrate alterations in levels of subunit protein in AD patients. Specifically, the α1 and β2/3 subunits of the $GABA_A$ receptor have been shown to be differentially affected in AD. Within vulnerable hippocampal sectors, reductions in the α1 subunit protein have been reported (Mizukami *et al.* 1998). Conversely, these studies have shown that the β2/3 subunits are relatively resistant to alteration in these AD patients (Mizukami *et al.* 1997b). Concomitant *in situ* hybridization studies demonstrated preservation in the β2 subunit mRNA, while significant reductions were seen in β3 subunit mRNA in AD patients (Mizukami *et al.* 1997a). In terms of γ subunits, compared with cognitively normal subjects, γ1/3 immunoreactivity was increased in end-stage AD subjects, and was specifically not localized to tangle bearing neurons (Iwakiri *et al.* 2009). Whether or not up-regulation or preserving γ1/3 and γ2 receptors somehow protects neurons against pathological alterations in tau is unknown, but several studies demonstrated that selective $GABA_A$ receptor agonists protective against Aβ-induced toxicity in rodents (Gu *et al.* 2003; Lin and Jun-Tian 2004; Louzada *et al.* 2004; Lee *et al.* 2005; Marcade *et al.* 2008). These neuroprotective effects could be blocked in culture by $GABA_A$ receptor antagonists (Marcade *et al.* 2008). As a potential mechanism underlying this effect, since Aβ has been reported to increase neuronal excitability by inhibiting GABA-induced Cl-current in neurons, these data suggest that $GABA_A$ modulators can normalize of Cl-flux (Lee *et al.* 2005). In addition, $GABA_A$ agonist treatment induces increased production of soluble APPα, indicating a shift toward increased α-secretase activity (Marcade *et al.* 2008).

In summary, with regard to AD-related changes, while there are inconsistencies, the literature generally supports the view that despite vast neuronal loss in AD, $GABA_A$ receptor subunits in the hippocampus of AD patients are relatively spared. The extent of this preservation appears to differ depending on the subunit. Mild reductions in α1, α5, β3 and modest reductions in GABA binding have been demonstrated. The potential significance of these reductions are discussed below.

Changes in DS

Of obvious interest for the pathogenesis of AD, is that which occurs in the content of DS. All individuals with DS show the neuropathological changes of AD by age 40 and most suffer cognitive decline by age 60 (Menendez 2005). In comparison with the aged and AD brain, considerably less has been done to document specific changes in $GABA_A$ receptors or subunit composition in the DS brain. During development, reports demonstrating change in neurogenesis and reduction in neuronal number in the cortex of DS patients is well established (Ross *et al.* 1984; Wisniewski et al. 1984; Becker *et al.* 1991; Golden and Hyman 1994). These changes are area, cell type and age specific, with the primary foci being small, granular, presumably GABAergic neurons in layer II and layer IV of the cortex (Ross *et al.* 1984). Studies demonstrate that cortical neuron density is normal in early gestation, but fewer neurons than normal exist in later gestation, and this reduction continues throughout early life (Golden and Hyman 1994; Weitzdoerfer *et al.* 2001). Cell culture studies of DS cortex neuronal progenitor cells (hNPCs) have found normal numbers of

neurons initially, but fewer neurons are present with time in culture, which is thought to be due to the fewer number of neurons generated (neurogenesis) and selective apoptosis of DS neurons (Busciglio and Yankner 1995). Microarray studies of DS hNPCs revealed gene changes indicative of defects in interneuron progenitor development. The expression of three $GABA_A$ receptor subtypes was altered; α2 was up-regulated, while α5 and α3 subunits were down-regulated (Bhattacharyya *et al*. 2009). Taken together, these changes in expression suggest that the DS progenitors may have inherent differences from normal cells that lead to decreased GABAergic interneuron neurogenesis.

Work in DS postmortem tissue also suggests an impaired balance between excitatory and inhibitory systems (Reynolds and Warner 1988; Risser *et al*. 1997; Seidl *et al*. 2001). More recent studies have found similar results in mouse models of DS, in which increased inhibition in the hippocampus was implicated in failed induction of long-term potentiation (Kleschevnikov *et al*. 2004). Furthermore, measurements made in hippocampal slices suggest reduced synaptic plasticity through a marked reduction in long-term potentiation in DS transgenic mice (Siarey *et al*. 1997; Galdzicki *et al*. 2001; Kleschevnikov *et al*. 2004; Belichenko *et al*. 2007). Because these deficits could be rescued by treating slices $GABA_A$ antagonists, the findings suggest an imbalance of neurotransmission manifested through increased inhibition. Significantly, reducing inhibitory neurotransmission in mouse models has been shown to enhance hippocampal-mediated cognitive tasks (Fernandez *et al*. 2007). Studies also suggest that changes in $GABA_A$ receptor composition occurs in DS model mice. Increases in localization of glutamic acid decarboxylase and vesicular GABA transporter have been documented (Belichenko *et al*. 2009). In contrast, no changes in glutamate transporter were seen. In terms of the composition of $GABA_A$ receptors, significant overall decreases $GABA_A$ receptor β2/3 subunit have been reported in the dentate gyrus early in the progression of pathology in DS mice, followed by a significant increase in months 3–8. Although no significant changes in α1 subunit was found, an alteration in the ratio of β2/3 to α1 was found in several areas of the hippocampus at 3 months of age (Belichenko *et al*. 2009), suggesting an increase in inhibitory neurotransmission with aging. To what extent the changes seen in DS reflect a similar pathogenetic process as that in AD is uncertain, but in both cases an increase in inhibitory neurotransmission can be suggested.

Pathobiology of AD relating to excitatory and inhibitory balance

A leading hypothesis in the AD field is the Aβ cascade hypothesis, which suggests that overproduction of Aβ is an initiator of multiple neurotoxic pathways, including excitotoxicity, oxidative stress, and cell death (Robinson and Bishop 2002). To what extent increased excitatory neurotransmission is responsible is uncertain. Indeed, recent studies demonstrate that glutamatergic signaling is compromised by Aβ-induced modulation of synaptic glutamate receptors in specific brain regions, paralleling early cognitive deficits in AD transgenic mice (Parameshwaran *et al*. 2008). Increasing Aβ can also elicit cortical and hippocampal seizure activity in AD mice, potentially caused by enhancement of GABAergic activity in the dentate gyrus (Palop *et al*. 2007; Minkeviciene *et al*. 2009). As a potential mechanism underlying this epileptic activity, studies demonstrate that Aβ can induce synaptic depression and aberrant E/I network synchronization (Palop and Mucke 2010). Although the relationship between these mechanisms and AD-related events are unclear, it seems likely that resultant synaptic depression and/or aberrations in E/I balance can lead to deficits in learning and memory and synaptic vulnerability in AD mouse models (Palop and Mucke 2010). Whether these changes play a causal role in cognitive impairment or pathology in humans has yet to be determined.

Importantly, the AD brain is characterized by modest decreases in $GABA_A$ subunit composition, which lends credence to the view that AD is a distinct pathological process from aging. The observation that sustained GABAergic neurotransmission exists in AD in face of excitatory failure would seem sufficient in itself to disrupt E/I balance. In our view, these changes exaggerated in DS, at least in animal models. We suggest that Aα plays a defining role for both disorders in creating an E/I balance through decreased pyramidal cell firing. It is interesting to consider that studies have found GABAergic receptors and signaling on these neurons unaffected (Kamenetz *et al*. 2003). This may result in a decrease in activation of downstream GABAergic neurons which may result in decreased inhibition of the inhibitory neurons that they innervate. The net result, in some circuits at least, would be decreased inhibition of these secondary inhibitory neurons with increased inhibition of the upstream excitatory neurons. Finally, Aβ may exert additional effects that impact the relative preservation and function of GABAergic neurons, as discussed above.

Potential avenues for treatment

The body of literature on $GABA_A$ receptors supports the notion that while massive cell loss may occur in AD, the net impact of this loss may be minimal. It seems reasonable to consider that to preserve hippocampal function, surviving hippocampal neurons begin to increase synthesis of $GABA_A$ receptor subunits so as to maintain inhibitory hippocampal circuitry. This concept of compensatory up-regulation of particular neurotransmitter receptor subunits in late-stage AD has been reported in the literature, with reductions in both NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subunits within vulnerable hippocampal sectors of the AD brain (for review, see Mishizen *et al*. 2000). Importantly, in these studies, the intensity of immunolabeling of the surviving cells was found to be equal, if not greater than subjects with little AD neuropathology. Furthermore, this increase in immunostaining was also greatly increased in non-vulnerable hippocampal sectors of AD brains. Such results have also been found in $GABA_A$ receptors subunits after unilateral transection of the perforant pathway (Mizukami *et al*. 1997c; Iwakiri *et al*. 2006). As we have discussed previously, it is therefore very possible that the relatively minimal net change seen in $GABA_A$ receptor subunits throughout the neuropathological progression of AD is caused by compensatory increases of the $GABA_A$ receptor subunits within surviving cells.

Importantly, work on the GABA system in AD has uncovered crucial links between Aβ and alterations in GABA signaling. These data not only serve to link GABA to the Aβ cascade hypothesis, but may shed light on the mechanisms behind increased seizure activity in AD. Aβ can reduce activity of the GABAergic system by inhibiting Cl-current into neurons and can induce seizure activity in AD mouse models. If we accept that GABAergic tone is relatively preserved in AD, future therapeutics aimed at increasing GABAergic activity may reduce production of Aβ, which can have two important disease-modifying effects; reducing or alleviating Aβ plaque development and Aβ-induced excitotoxity, both of which increase cognition.

In conclusion, the general literature indicates that $GABA_A$ receptors are potential targets for treatment of both cognitive deficits and seizure activity in AD and DS. Still, validation of potential $GABA_A$ therapeutics needs to be tested and validated in currently available DS and AD mouse models and in banked postmortem human tissues. Results collected thus far on $GABA_A$ receptors in aging, DS and AD provide documentation of the alterations of inhibitory circuitry, but also exemplifies the dynamic plasticity intrinsic to the adult brain even during neurodegenerative disease progression.

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Abbreviations used

Aβ, β-amyloid

AD, Alzheimer's disease

DS, Down syndrome

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