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REVIEW

$GABA_A$ receptor diversity and pharmacology

H. Möhler

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Abstract Because of its control of spike-timing and oscillatory network activity, γ-aminobutyric acid (GABA)-ergic inhibition is a key element in the central regulation of somatic and mental functions. The recognition of $GABA_A$ receptor diversity has provided molecular tags for the analysis of distinct neuronal networks in the control of specific pharmacological and physiological brain functions. Neurons expressing α_1GABA_A receptors have been found to mediate sedation, whereas those expressing α_2GABA_A receptors mediate anxiolysis. Furthermore, associative temporal and spatial memory can be regulated by modulating the activity of hippocampal pyramidal cells via extrasynaptic α_5GABA_A receptors. In addition, neurons expressing α_3GABA_A receptors are instrumental in the processing of sensory motor information related to a schizophrenia endophenotype. Finally, during the postnatal development of the brain, the maturation of GABAergic interneurons seems to provide the trigger for the experience-dependent plasticity of neurons in the visual cortex, with α_1GABA_A receptors setting the time of onset of a critical period of plasticity. Thus, particular neuronal networks defined by respective $GABA_A$ receptor subtypes can now be linked to the regulation of various clearly defined behavioural patterns. These achievements are of obvious relevance for the pharmacotherapy of certain brain disorders, in particular sleep dysfunctions, anxiety disorders, schizophrenia and diseases associated with memory deficits.

H. Möhler (✉)
Institute of Pharmacology and Department of
Chemistry and Applied Biosciences,
University and ETH Zurich,
Winterthurerstrasse 190,
Zürich CH-8057, Switzerland
e-mail: mohler@pharma.unizh.ch

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Inhibitory interneurons

The activity of inhibitory interneurons, most of which are γ-aminobutyric acid (GABA)-ergic, is thought to set the spatio-temporal conditions required for the various patterns of network oscillations that may be critical for information processing (O'Keefe and Nadel 1978; O'Keefe and Recce 1993; Skaggs et al. 1996; Paulsen and Moser 1998; Engel et al. 2001; Harris et al. 2002; Mehta et al. 2002; Traub et al. 2002; Klausberger et al. 2003).

Diversity of interneurons

To achieve a strict time control of principal cells, GABAergic interneurons display several remarkable features. (1) Their action potential is traditionally faster than that of pyramidal cells and the kinetics of synaptic events that excite inhibitory cells are faster than those that excite pyramidal cells (Martina et al. 1998; Geiger et al. 1997). (2) GABAergic interneurons are morphologically highly diverse, which reflects their multiple functions in neuronal networks (Gupta et al. 2000; Markram et al. 2004; Monyer and Markram 2004). (3) These interneurons show a domain-specific innervation of principal cells; thus, depending on the type of interneuron, particular input domains of pyramidal cells can be selectively regulated and, similarly, the output of pyramidal cells can be specifically regulated by axo-axonic GABAergic interneurons. (4) The response properties of interneuron signalling is shaped by the type of $GABA_A$ receptor expressed synaptically or extrasynaptically. For instance,

the soma of hippocampal pyramidal cells is innervated by two types of basket cells: the fast spiking parvalbumin-containing basket cells form synapses containing α_1GABA$_A$ receptors, which display fast kinetics of deactivation (Nyíri et al. 2001; Klausberger et al. 2002; Freund and Buzsaki 1996; Pawelzik et al. 2002), whereas the synapses of the regular spiking cholecystokinin (CCK)-positive basket cells contain α_2GABA$_A$ receptors, which display slower kinetics than α_1 receptors (Nyíri et al. 2001; Brussaard and Herbison 2000; Hutcheon et al. 2000; Jüttner et al. 2001; Vicini et al. 2001). Axon initial segments of principal cells also contain α_2 receptors, which appear to be kinetically sufficient for simple on/off signalling. Furthermore, distinct GABA$_A$ receptors are segregated to synaptic and extra-synaptic membranes (Nusser et al. 1998; Fritschy and Brünig 2003). Thus, functionally specialized interneurons operate with the kinetically appropriate GABA$_A$ receptor subtypes to regulate network behaviour (Fig. 1, Table 1). Since GABAergic interneurons are operative throughout the brain, a highly diverse repertoire of GABA$_A$ receptors is required.

Retrograde regulation of GABAergic interneurons

Retrograde signalling adds another level of complexity to the regulation of interneuron activity. The terminals of CCK-positive GABAergic basket cells in hippocampus and amygdala contain CB1-cannabinoid receptors (Katona et al. 1999, 2001). These receptors mediate depolarisation-induced suppression of inhibition (DSI) (Pitler and Alger 1994; Alger and Pitler 1995). This phenomenon is due to endocannabinoids which emanate from the postsynaptic cell and act as retrograde signal (Wilson and Nicoll 2001; Maejima et al. 2001). The depolarization of hippocampal pyramidal cells (Pitler and Alger, 1992) and of cerebellar Purkinje cells (Llano et al. 1991) results in a transient decrease in the release of GABA from inhibitory terminals that contain CB1-receptors and synapse onto the depolarized cells (Vincent and Marty, 1993; Pitler and Alger, 1994; Alger and Pitler, 1995).Both the DSI in the hippocampus (Wilson and Nicoll 2001; Maejima et al. 2001) and the cerebellum (Kreitzer and Regehr 2001a,b) are the result of activity-dependent de-novo synthesis and release of endo-

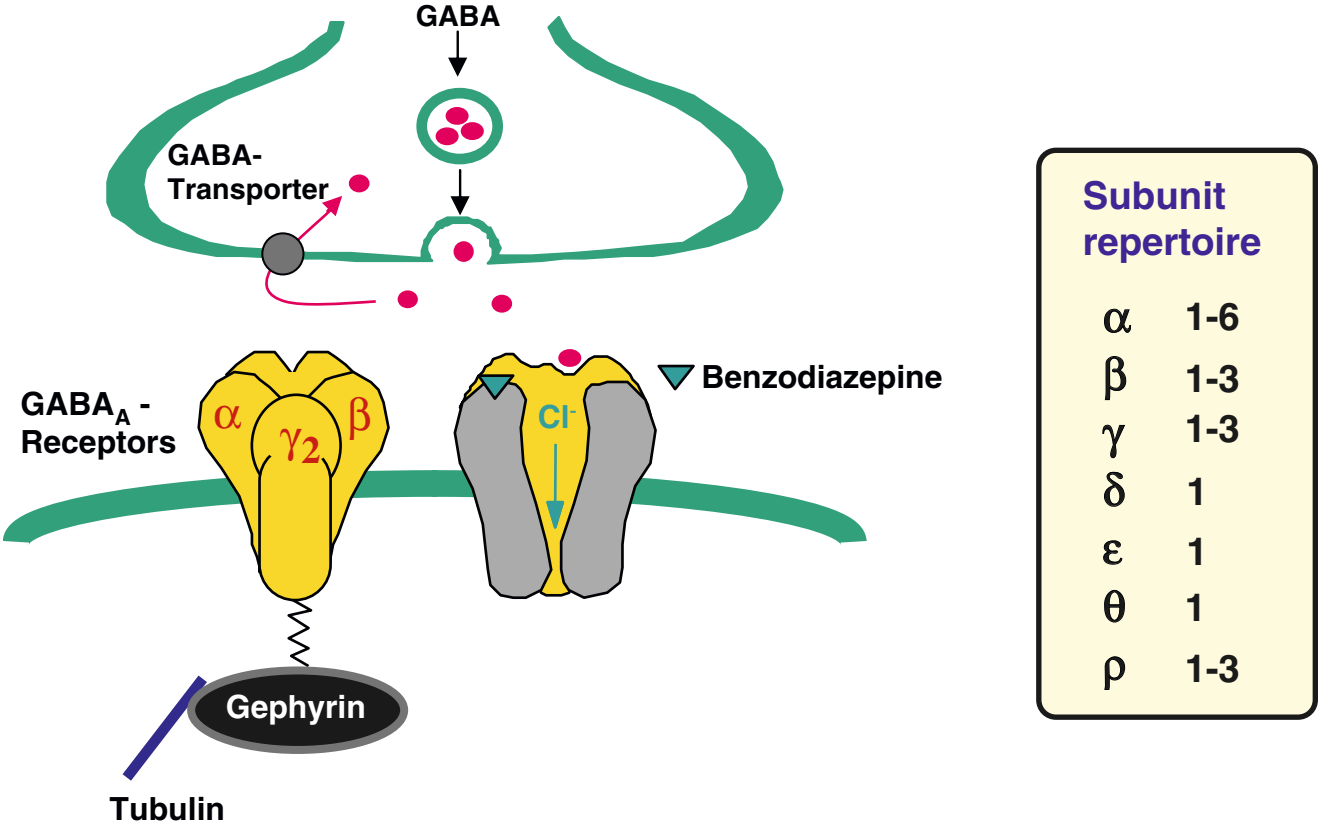

Fig. 1 Representation of a GABAergic synapse depicting major elements of signal transduction. GABA$_A$ receptors are heteromeric membrane proteins linked by an as yet unknown mechanism to the synaptic anchoring protein, gephyrin, and the cytoskeleton. The sequence of subunits corresponds to a modelling proposal (Ernst et al. 2003). The binding sites for GABA and benzodiazepines are located at the interface of the α/β and α/γ_2 subunits, respectively. Synaptic GABA$_A$ receptors mediate phasic inhibition providing a rapid point-to-point communication for synaptic integration and control of rhythmic network activities. Extrasynaptic GABA$_A$ receptors (not shown) are activated by synaptic spillover or the non-vesicular release of GABA. By mediating tonic inhibition, they provide a maintenance level of reduction in neuronal excitability (Mody and Pearce 2004; Möhler et al. 2005)

Table 1 $GABA_A$-receptor subtypes (compiled from Möhler et al. 2002; Fritschy and Brünig 2003)

Composition	Pharmacological characteristics	Regional and neuronal localisation	Subcellular localization
$\alpha_1\beta_2\gamma_2$	Major subtype (60 % of all $GABA_A$ receptors). Mediates the sedative, amnestic and, to a large extent, the anticonvulsant action of benzodiazepine site agonists. High affinity for classical benzodiazepines, zolpidem and the antagonist flumazenil	Cerebral cortex (layer 1–VI, selected interneurons and principal cells); hippocampus (selected interneurons and principal cells); pallidum striatum (interneurons); thalamic relay nuclei; olfactory bulb (mitral cells and interneurons); cerebellum (Purkinje cells and granule cells); deep cerebellar nuclei; amygdala; basal forebrain; substantia nigra pars reticulata; inferior colliculus; brainstem	Synaptic (soma and dendrites) and extrasynaptic in all neurons with high expression
$\alpha_2\beta_3\ \gamma_2$	Minor subtype (15–20%). Mediates anxiolytic action of benzodiazepine site agonists. High affinity for classical benzodiazepine agonists and the antagonist flumazenil. Intermediate affinity for zolpidem	Cerebral cortex (layers I–IV) hippocampal formation (principal cells mainly on the axon initial segment); olfactory bulb (granule cells); striatum (spiny stellate cells); inferior olivary neurons (mainly on dendrites); hypothalamus; amygdala (principal cells); superior colliculus; motor neurons	Mainly synaptic, enriched in axon initial segment of cortical and hippocampal pyramidal cells
$\alpha_3\beta_n\gamma_2$	Minor subtype (10–15%). High affinity for classical benzo-diazepine agonists and the antagonist flumazenil. Intermediate affinity for zolpidem	Cerebral cortex (principal cells in particular in layers V and VI; some axon initial segments); hippocampus (some hilar cells); olfactory bulb (tufted cells); thalamic reticular neurons; cerebellum (Golgi type II cells); medullary reticular formation; inferior olivary neurons; amygdala; superior colliculus; brainstem; spinal cord; medial septum; basal forebrain cholinergic neurons; raphe and locus coeruleus (serotoninergic and catecholaminergic neurons)	Mainly synaptic, including some axon initial segments; extrasynaptic in inferior olivary neurons
$\alpha_4\beta_n\delta$	Less than 5 % of all receptors. Insensitive to classical benzodiazepine agonists and zolpidem	Dentate gyrus (granule cells); thalamus	Extrasynaptic (no direct morphological evidence)
$\alpha_5\beta_3\gamma_2$	Less than 5% of all receptors; high affinity for classical benzodiazepine agonists and the antagonist flumazenil. Low affinity for zolpidem	Hippocampus (pyramidal cells); olfactory bulb (granule cells, periplomerular cells); cerebral cortex; amygdala; hypothalamus; superior colliculus; superior olivary neurons; spinal trigeminal neurons; spinal cord	Extrasynaptic in hippocampus, cerebral cortex, and olfactory bulb; synaptic and extrasynaptic in spinal trigeminal nucleus and superior olivary nucleus
$\alpha_6\beta_{2,3}\gamma_2$	Less than 5 % of all receptors. Insensitive to classical $\alpha_6\beta_{2,3}\delta$ benzodiazepine agonists and zolpidem. Minor population. Lacks benzodiazepine site	Cerebellum (granule cells); dorsal cochlear nucleus	Synaptic (cerebellar glomeruli) and extrasynaptic on granule cell dendrites and soma

cannabinoids from the postsynaptic neuron. By interacting with CB1 receptors, the calcium influx into the presynaptic terminal is reduced (Kreitzer and Regehr 2001a; Caulfield and Brown 1992) resulting in a decrease of GABA release. Pharmacologically, the inhibition of the degradation of anandamide resulted in an CB1 receptor-mediated anxiolytic response (Kathuria et al. 2003). Recently, endocannabinoids were shown to mediate not only transient, but also long term changes in inhibitory synaptic transmission. Endocannabinoid production, stimulated through metabotropic glutamate receptor activation in hippocampal pyramidal cells, caused a long lasting reduction in GABAergic signaling onto the pyramidal cells (Chevaleyre and Castillo 2003). A similar change in long-term synaptic plasticity of

the GABAergic system was observed in the amygdala. The release of endocannabinoids in the basolateral amygdala contributed to the extinction of aversive memory based on a long lasting decrease of GABAergic signalling (Marsicano et al. 2002). Thus, CB1 receptor activation in the hippocampus, amygdala and possibly other parts of the brain result in reduced levels of anxiety. This is due to either a transient depression of GABA release or a modulation of long term plasticity at the respective synapses. In addition, endocannabinoids act as retrograde signals at excitatory glutamatergic synapses where they mediate a depolarisation-induced suppression of excitation (Kreitzer and Regehr 2001a) which may also contribute to their behavioral effects.

Structure of $GABA_A$ receptors

Like other members of the nicotinic superfamily of ligand-gated ion channels, ionotropic GABA receptors are considered to consist of 5 protein subunits arranged around a central pore that constitutes the actual ion channel. Each subunit has a large extracellular N-terminal domain which incorporates part of the agonist/antagonist binding site, followed by three membrane spanning domains (M1-3), an intracellular loop of variable length and a fourth membrane spanning domain (M4), with the C-terminal end being extracellular. Each subunit arranges itself such that the second membrane-spanning domain (M2) forms the wall of the channel pore. The cytoplasmic loop, between the third and fourth transmembrane domains (M3 and M4), is believed to be the target for protein kinases, required for subcellular targeting and membrane clustering of the receptor. There are 16 different subunits comprising the $GABA_A$ receptor family: α_{1-6}, β_{1-3}, γ_{1-3}, δ, ε, π and θ. In addition, there are splice variants of many of these subunits. Based on this subunit repertoire more than 2000 different $GABA_A$ receptors could exist if the subunit combinations were restricted to those containing two α, two β and one other subunit. In fact, studies of native $GABA_A$ receptors suggest that there may be less than 20 widely occurring $GABA_A$ receptor subtype combinations, with the major combinations being $\alpha_1\beta_{2/3}\gamma_2$, $\alpha_2\beta_3\gamma_2$, $\alpha_3\beta_3\gamma_2$ (for review Barnard et al. 1998; Whiting et al. 2000; Sieghart and Sperk 2002; Möhler et al. 2000, 2002, 2005; Möhler 2001, 2002; Fritschy et al. 2004; Rudolph and Möhler 2006) (Table 1).

In the retina homomeric receptors consisting of the ρ subunit represent a particular class of GABA gated chloride channels. Their GABA site is insensitive to bicuculline and baclofen and they are not modulated by barbiturates or benzodiazepines. Due to these distinctive features the receptors are sometimes termed $GABA_c$-receptors (Bormann 2000), although they are a homomeric class of $GABA_A$-receptors (Barnard et al. 1998).

The physiological significance of the structural diversity of $GABA_A$ receptors lies in the provision functionally diverse of receptors which differ in their channel kinetics, affinity for GABA, rate of desensitization and ability for transient chemical modification such as phosphorylation. In addition, $GABA_A$ receptor subtypes differ in their topology in neuronal networks in that they show a cell-type specific expression and-in case of multiple receptor subtypes present in a neuron-a domain-specific location (Table 1).

Pharmacology of $GABA_A$ receptors

Diazepam-sensitive $GABA_A$ receptors

Receptors containing the α_1, α_2, α_3 or α_5 subunits in combination with any of the β subunits and the γ_2 subunit are most prevalent in the brain. These receptors are sensitive to benzodiazepine modulation. The major receptor subtype is assembled from the subunits $\alpha_1\beta_2\gamma_2$, with only a few brain regions lacking this receptor (e.g. granule cell layer of the olfactory bulb, reticular nucleus of the thalamus, spinal cord motoneurons) (Fritschy and Mohler 1995; Pirker et al. 2000, Fritschy and Brünig 2003).

Receptors containing the α_2 or $\alpha_3$subunit are considerably less abundant and are highly expressed in brain areas where the α_1 subunit is absent or present at low levels. The α_2 and α_3 subunits are frequently coexpressed with the β_3 and γ_2 subunits which is particularly evident in hippocampal pyramidal neurons ($\alpha_2\beta_3\gamma_2$) and in cholinergic neurons of the basal forebrain ($\alpha_3\beta_3\gamma_2$). The α_3 $GABA_A$ receptors are the main subtypes expressed in monoaminergic and basal forebrain cholinergic cells (Gao et al. 1993) and are, in addition, strategically located in the thalamic reticular nucleus for modulating the thalamo-cortical circuit (Huntsmann et al. 1999). Marked differences in desensitization kinetics have been reported between synaptic α_2-and extrasynaptic α_3-receptors whereby the latter desensitize very slowly (Devor et al. 2001). The factors regulating $GABA_A$ receptor kinetics at synaptic and extrasynaptic sites are yet unknown (Moss and Smart 2001). The ligand-binding profile of the α_2-and α_3-receptors differs from that of $\alpha_1\beta_2\gamma_2$ by having a considerably lower displacing potency for ligands such as βCCM, CL 218,872, and zolpidem.

Receptors containing the α_5 subunit are of minor abundance in the brain but are expressed to a significant extent in the hippocampus, where they comprise 15 % to 20 % of the diazepam-sensitive $GABA_A$ receptor population, predominately coassembled with the β_3 and γ_2 subunits. Pharmacologically, the α_5-receptors are differentiated from

$\alpha_1\beta_2\gamma_2$, $\alpha_2\beta_3\gamma_2$ and $\alpha_3\beta_3\gamma_2$ receptors by a lower affinity to CL 218, 872 and near-insensitivity to zolpidem.

The subunits γ_1 and γ_3 characterize a small population of receptors that contain various types of α and β subunits. Due to their reduced affinity for the classical benzodiazepines they do not appear to contribute to any great extent to their pharmacology in vivo.

It should be kept in mind that complex benzodiazepine actions such as the development of tolerance can implicate more than a single receptor subtype. For instance, while the sedative action of diazepam is mediated by α1 $GABA_A$ receptors (see below), the development of tolerance to this action under chronic diazepam treatment requires the interaction with both α1 $GABA_A$ receptors and α5 $GABA_A$ receptors (van Rijnsoever et al. 2004).

Diazepam-insensitive $GABA_A$ receptors

$GABA_A$ receptors that do not respond to clinically used ligands such as diazepam, flunitrazepam, clonazepam, and zolpidem are of low abundance in the brain and are largely characterized by the α_4 and α_6 subunits. Receptors containing the α_4 subunit are generally expressed at very low abundance but more prominently in thalamus and dentate gyrus (Pirker et al. 2000); those containing the α_6 subunit are restricted to the granule cell layer of the cerebellum (about 30–50 % of all $GABA_A$ receptors in the cerebellum; Nusser et al. 1996; Pöltl et al. 2003). Both receptor populations are structurally heterogeneous, and the majority of the α_6-containing receptors contain the γ_2 subunit in the $\alpha_6\alpha_1\beta_2\gamma_2$ subunit combination (Pöltl et al. 2003). Apart form the lack of affinity of classical benzodiazepines, the benzodiazepine-site profile of α_4 and α_6 receptors is characterized by a low affinity for flumazenil and bretazenil and an agonistic efficacy of Ro 15-4513 and bretazenil (Benson et al. 1998). The δ subunit is frequently coassembled with the α_4 or the α_6 subunit in benzodiazepine insensitive receptors (Möhler et al. 2000; Whiting et al. 2000; Möhler 2001). Receptors containing the δ subunit are located exclusively at extrasynaptic sites as shown in dentate gyrus and cerebellum. They are tailor made for tonic inhibition, due to their high affinity for GABA and slow desensitization kinetics (Brickley et al. 1996, 2001).

$GABA_A$ receptor subtypes: a new pharmacology

The selective pattern of expression of $GABA_A$ receptor subtypes opened the possibility to modulate distinct neuronal circuits, provided novel ligands were found which displayed a differential interaction with $GABA_A$ receptor subtypes based on either selective affinity or selective efficacy (Table 2). Such agents would be expected to display therapeutic indications which are more selective than those of the classical benzodiazepines and go beyond their spectrum of activity.

The dissection of receptor pharmacology has been achieved experimentally by generating four lines of point-mutated mice in which the receptors containing the α_1, α_2, α_3 or α_5 subunits, respectively, are rendered diazepam-insensitive by replacing a conserved histidine residue (H) in the drug-binding domain by an arginine (R; Benson et al. 1998; Rudolph et al. 1999; Löw et al. 2000; Crestani et al. 2002). In the respective point-mutated mice, the pharmacological action linked to the point-mutated receptor should be missing and thereby reveal the pharmacological relevance of the respective receptor in wild-type mice. Since the subunit composition and distribution of $GABA_A$ receptor subtypes are largely conserved between rodents and non-human primates, the results are thought to be relevant to the human condition (Rudolph and Möhler 2004).

$GABA_A$ receptors for sedation and sleep

Frequently, sedation is taken as a surrogate marker for hypnotic activity. The sedative component of benzodiazepines, measured by the reduction of locomotor activity, has been attributed to neuronal circuits expressing α_1GABA_A receptors, the most prevalent receptor subtype in the brain. Mice in which the α_1GABA_A receptor has been rendered diazepam-insensitive by a point mutation [α_1(H101R)] fail to be sedated by diazepam (Rudolph et al. 1999; McKernan et al. 2000). Ligands with a preferential affinity for α_1 receptors such as zolpidem or zaleplon are used as hypnotics (Table 2). Similarly, the changes in the electroencephalogram (EEG) pattern induced by zolpidem in wild-type mice are almost exclusively mediated via α_1GABA_A receptors (Kopp et al. 2004a). However, the changes in sleep architecture (suppression of rapid eye movement or REM sleep) and EEG-frequency profiles (reduction of slow-wave sleep, increase in fast β-frequencies) induced by classical benzodiazepines are largely attributable to effects mediated by receptors others than α_1 (Tobler et al. 2001). The enhancement of α_2GABA_A receptors by diazepam appears to have the most pronounced effect on the sleep EEG in wild-type mice. When the α_2GABA_A receptor is rendered diazepam-insensitive by a point mutation [α_2(H101R)], the diazepam-induced suppression of δ-waves, the increase in fast β-waves in non-REM sleep (>16 Hz) and the diazepam-induced increase of θ-waves in REM sleep are strongly attenuated (Kopp et al. 2004b). Thus, the hypnotic EEG fingerprint of diazepam can be dissociated from its sedative action. Future hypnotics might target changes in the EEG pattern, which are characteristic of physiological sleep, and thereby aim at improving sleep quality. For instance, the GABA-mimetic gaboxadol (4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridine-3-0l hydrochlo-

Table 2 $GABA_A$ receptor subtype ligands*

Drug	Main activity	Interaction with recombinant $GABA_A$ receptors[1,2]	Reference
A.Benzodiazepine site ligands			
Zolpidem	Hypnotic	Preferential affinity for α_1	Dämgen and Lüddens, 1999
Zaleplone	Hypnotic	Preferential affinity for α_1	Dämgen and Lüddens, 1999
Indiplon	Hypnotic	Preferential affinity for α_1	Foster et al. 2004
L-838 417	Anxiolytic	Comparable affinity at α_1, α_2, α_3, α_5 subtype. Partial agonist at α_2, α_3, α_5 (not α_1) subtype	McKernan et al. 2000
Ocinaplon	Anxiolytic	Comparable affinity at α_1 α_2, α_3, α_5 subtype. Partial agonist at α_2, α_3, α_5 subtype nearly full agonist at α_1	Lippa et al. 2005
SL 651 498	Anxiolytic	Agonist at α_2, α_3, partial agonist at α_1 and α_5 subtype	Griebel et al. 2003
TPA 023	Anxiolytic	Partial agonist at α_2, α_3 subtypes, antagonist at α_1, α_5 subtypes	Atack et al. 2006a
TPA 003	Anxiolytic	Partial agonist at α_3 subtype	Dias et al. 2005
ELB 139	Anxiolytic	Selective receptor profile uncertain	Langen et al. 2005
L-655 708	Memory enhancer, Anxiogenic	Partial inverse agonist with preference for α5 subtype	Sternfeld et al. 2004; Chambers et al. 2004; Navarro et al. 2002, 2004
α_3 IA	Anxiogenic	Weak inverse agonist at α_3	Atack et al. 2005
B. Modulatory site other than benzodiazepine site			
Ethanol	Anxiolytic Sedative	High sensitivity (≥3 mM) at $\alpha_4(\alpha_6)\beta_{3\delta}$[3]; Medium sensitivity (≥30 mM) at $\alpha_4(\alpha_6)\beta_{2\delta}$[3]; Low sensitivity (≥100 mM) at $\alpha_4(\alpha_6)\beta_3\gamma_2$	Wallner et al. 2003
Neurosteroids (e.g. 3α, 5α-THDOC)	Anxiolytic Sedative Anaesthetic	High sensitivity at δ-containing subtypes [3] and at α_1, α_3 receptors in combination with β_1	Belelli and Lambert 2005
Intravenous anaesthetics (Etomidate Propofol)	Sedative Anaesthetic	Act on receptor subtypes containing β_3 i.e. mainly α_2 and α_3 subtypes	Rudolph and Antkowiak 2004
C. GABA site			
Gaboxadol	Hypnotic	Partial agonist at α_1, α_3 subtypes full agonist at α_5 and superagonist at $\alpha_4\beta_3\delta$ receptors[2]	Stornstovu and Ebert 2003

*This table is a modified version from Rudolph and Möhler (2006)

[1]Classical partial agonists that do not differentiate between $GABA_A$ receptor subtypes such as Bretazenil (Haefely et al. 1990) or Pagoclone (Atack et al. 2006b) are not considered in this review.

[2]Data should be treated with caution as properties of recombinant receptors that are expressed in foreign host cells might not give an accurate reflection of their neuronal counterparts.

[3]GABA is a weak partial agonist on δ-containing receptors, which largely explains the strong modulatory response of ligands acting on δ-containing receptors (Bianchi and MacDonald 2003). THDOC, 5α-pregnane3α,21-diol-20-one.

ride; synonym THIP), which interacts preferentially with $\alpha_4\beta_3\delta$ $GABA_A$ receptors in vitro (Brown et al. 2002; Storustovu and Ebert 2003) has been found to enhance slow-wave sleep in vivo (Lancel and Steiger 1999; Huckle 2004).

$GABA_A$ receptors for anxiolytic action

Since α_1GABA_A receptors were found to mediate sedation but not anxiolysis (Rudolph et al. 1999; McKernan et al. 2000), the anxiolytic activity of benzodiazepines was expected to reside in one or several of the remaining benzodiazepine-sensitive $GABA_A$ receptors (α_2, α_3, α_5). The differentiation of $GABA_A$ receptors by knock-in point mutations showed that the α_2 receptor, but not the α_3 or α_5GABA_A receptor, mediated the anxiolytic activity of diazepam (Löw et al. 2000; Crestani et al. 2002). In α_2(H101R) mice, but not in α_3(H126R) or α_5(H105R) mice, diazepam failed to induce anxiolytic activity (light-dark paradigm, elevated plus maze). With respect to the α_2GABA_A receptor, a highly selective target for the anxiolytic activity of benzodiazepine tranquillizers had

been identified. In keeping with this notion, the benzodiazepine site ligand L-838417, which exhibited efficacy at α_2, α_3 and α_5 but not α_1GABA_A receptors, proved to be anxiolytic in wild-type rats (Table 2; McKernan et al. 2000). Similarly, partial agonists of 3-heteroaryl-2-pyridones acting at the benzodiazepine site with efficacy at α_2, α_3 and α_5 receptors, but not at α_1 receptors, were found to show anxiolytic activity in rodents (Table 2; Collins et al. 2002). Nevertheless, the extent to which the α_3GABA_A receptor component contributed to the anxiolytic activity of these ligands remained to be clarified. In mice that lacked α_3GABA_A receptors, the anxiolytic activity of diazepam was undiminished (Yee et al. 2005). However, an α_3-selective inverse agonist was anxiogenic and proconvulsant in rodents (Table 2; Collins et al. 2002). In addition, TP003 with selective efficacy at the α_3GABA_A receptor was anxiolytic, although only at high receptor occupancy (Dias et al. 2005). Classical benzodiazepines exert anxiolysis at low receptor occupancy suggesting that the α_2GABA_A receptors, and not the α_3GABA_A receptors, are the major mediators of this activity. The contribution of α_3GABA_A receptors is unlikely to be of major relevance. Thus, the strategy to develop novel daytime anxiolytics, which are free of sedation, is clear (Whiting 2003; Möhler et al. 2002; Möhler et al. 2005).

The α_2GABA_A receptors by their preponderant localization on the axon-initial segment of principal cells in the cerebral cortex and hippocampus can control the output of these cells. In addition, among α_1, α_2 and α_3GABA_A receptors, α_2 receptors are prominent in the central nucleus of the amygdala, a key area for the control of emotions, whereas α_1GABA_A receptors are totally absent (Marowsky et al. 2004). Thus, by their strategic distribution in brain areas involved in anxiety responses, α_2GABA_A receptors represent key substrates for anxiolytic drug action.

$GABA_A$ receptors for learning and memory

Hippocampal pyramidal cells express various structurally diverse $GABA_A$ receptors in a domain-specific manner. Whereas α_1 and α_2GABA_A receptors are largely synaptic, α_5GABA_A receptors are located extrasynaptically at the base of the spines and on the adjacent shaft of the pyramidal cell dendrite. The α_5GABA_A receptors are therefore in a privileged position to modulate the excitatory input arising at the spines via N-methyl-D-aspartate (NMDA) receptors. The introduction of a point mutation (H105R) into the α_5 subunit is associated with a specific reduction of the hippocampal α_5-subunit-containing $GABA_A$ receptors, whereas the pattern of distribution is undisturbed (Crestani et al. 2002). Mice with a partial deficit of α_5GABA_A receptors in the hippocampus show an improved performance in trace fear conditioning, a hippocampus-dependent memory task (Crestani et al. 2002). In addition, these mutants display a resistance to the extinction of conditional fear over several days (Yee et al. 2004). Similarly, in a mouse line in which α_5GABA_A receptors are absent in the entire brain (Collinson et al. 2002; Whiting 2003), improved performance has been observed in the water maze model of spatial learning. Furthermore, a partial inverse agonist acting at α_5GABA_A receptors enhances the performance of wild-type rats in the water maze test (Chambers et al. 2003; Table 2). Thus, neuronal inhibition in the hippocampus mediated via α_5GABA_A receptors is a critical element in the regulation of the acquisition and expression of associative memory. Of note, the behavioural consequences of an impairment of α_5GABA_A receptors are opposite to those of an NMDA receptor deficit as shown in spatial and temporal associative memory tasks. Thus, these two receptor systems seem to play a complementary role in controlling signal transduction at the hippocampal principal cells.

$GABA_A$ receptors for sensorimotor processing

A deficit in GABAergic inhibitory control is one of the major hypothesis underlying the symptomatology of schizophrenia (Lewis et al. 2005). A potential contribution of $GABA_A$ receptor subtypes has therefore been investigated with regard to the overactivity of the dopaminergic system, an overactivity considered to be a major factor in schizophrenia. The dopaminergic system is under GABAergic inhibitory control mainly via α_3-containing $GABA_A$ receptors (Fritschy and Möhler 1995; Pirker et al. 2000). Their functional role has been explored in mice lacking the α_3 subunit gene. Mice with an α_3-knockout display no adaptive changes in the expression of α_1, α_2 and α_5 subunits and their anxiety-related behaviour is normal. However, they exhibit a marked deficit in prepulse inhibition of the acoustic startle reflex, pointing to a deficit in sensorimotor information processing (Yee et al. 2005). This deficit in prepulse inhibition is normalized by the administration of the antipsychotic dopamine D2-receptor antagonist haloperidol, suggesting that the behavioural phenotype is caused by hyperdopaminergia (Yee et al. 2005). Attenuation of prepulse inhibition is a frequent phenotype of psychiatric conditions, including schizophrenia. These results suggest that α_3-selective agonists might constitute an effective treatment for sensorimotor gating deficits in various psychiatric conditions, a view supported by the observation that the partial benzodiazepine-site agonist bretazenil, in earlier open clinical trials, displayed an antipsychotic activity similar to neuroleptic drugs (Delini-Stula and Berdah Tordjman 1996). The α_3-selective agonists might lack the sedative or extrapyramidal side-effects of classical neuroleptics and would thus be valuable agents.

Among various brain structures, the hippocampus is believed to play an important role in the modulation of prepulse inhibition. In α_5(H105R) point-mutated mice, the expression of the α_5 subunit containing $GABA_A$ receptors in the hippocampus is reduced (see above; Crestani et al. 2002). In these animals, prepulse inhibition is attenuated concomitant with an increase in spontaneous locomotor activity (Hauser et al. 2005). Thus, the α_5-subunit-containing $GABA_A$ receptors, which are located extrasynaptically and are thought to mediate tonic inhibition, are important regulators of the expression of prepulse inhibition and locomotor exploration. Post-mortem analyses of brains from patients with schizophrenia have consistently revealed structural abnormalities of developmental origin in the hippocampus (Lewis et al. 2005). Such abnormalities may include disturbances of α_5GABA_A receptor function given that schizophrenic patients are known to exhibit a deficit in prepulse inhibition. Thus, agonists acting on both α_3 and α_5GABA_A receptors may be beneficial in overcoming this endophenotypic manifestation of the disease.

$GABA_A$ receptors for anaesthetic action

The targets that mediate the clinical effects of general anaesthetics are largely unknown (Campagna et al. 2003; Rudolph and Antkowiak 2004). Recent work has focused on the role of $GABA_A$ receptors, with studies being based on the analysis of point-mutated knock-in mice carrying point mutations in the β_3 and β_2 subunits of the $GABA_A$ receptor. These mutations render the $GABA_A$ receptors containing the respective subunits insensitive to modulation by etomidate, propofol and certain volatile anaesthetics, such as enflurane. The β_3-containing $GABA_A$ receptors have been found to mediate the immobilizing action of etomidate and propofol apparently in full (Table 2; Jurd et al. 2003) and of enflurane, isoflurane and halothane in part (Jurd et al. 2003; Lambert et al. 2005; Liao et al. 2005). In addition, they mediate part of the hypnotic action of etomidate and propofol (Jurd et al. 2003) but apparently not of the volatile anaesthetics (Jurd et al. 2003; Lambert et al. 2005). In contrast, the hypnotic action of etomidate is mediated by β_2-containing $GABA_A$ receptors (Reynolds et al. 2003). Further studies have revealed that the respiratory depressant action of etomidate and propofol is also mediated by β_3-containing $GABA_A$ receptors, whereas the heart-rate depressant action and, to a large part, the hypothermic action of etomidate and propofol are mediated by other targets (Zeller et al. 2005; Cirone et al. 2004). Thus, a β_3-selective agent would be predicted to be immobilizing and respiratory depressant but would largely lack the heart-rate depressant and hypothermic actions of etomidate and propofol. The analysis of α subunits involved in mediating the actions of general anaesthetics is expected to result in further insights into the contribution of $GABA_A$ receptors to anaesthesia. Mutations in α subunits have been identified in recombinant studies that render $\alpha_x\beta_x\gamma_2$ $GABA_A$ receptors insensitive to specific volatile anaesthetics but not to etomidate or propofol (Mihic et al. 1997; Krasowski et al. 1998). Studies with knock-in mice carrying these mutations are expected to yield information as to the contribution of individual $GABA_A$ receptors subtypes and the $GABA_A$ receptor family as a whole to the action of volatile general anaesthetics.

$GABA_A$ receptors controlling postnatal development

Apart from its trophic role in embryonal development (Represa and Ben-Ari 2005), GABA is a major determinant for postnatal developmental plasticity; this has been investigated in various sensory systems. For instance, in the rodent somatosensory system, axons from each whisker form a somatotopic map in the cortex, known as the barrel map. During a critical period of neonatal development, this barrel map is fine-tuned in response to sensory experience based on a variety of synaptic mechanisms involving not only excitatory, but also inhibitory circuits (Foeller and Feldmann 2004). The role of inhibitory circuits in synaptic reorganization is similarly apparent in the auditory system. Recent work has revealed a dramatic remodelling of inhibitory synapses shortly after the onset of hearing (aural dominance bands). The restructuring relies on both spontaneous and sensory-evoked neural activity (Kandler 2004). In the postnatal visual system, the role of GABA has been investigated in detail.

In the visual system, developmental plasticity is most apparent in the formation of ocular dominance columns in layer IV of the primary visual cortex. Cortical territories receiving neuronal input from one eye alternate with territories from the other eye. Initially, at birth, the thalamic inputs from both eyes to the visual cortex are totally overlapping (Ferster 2004). The separation of the visual inputs into ocular dominance columns only arises in the subsequent phase of remodeling. This process is sensitive to light as shown by classical work on the influence of monocular deprivation on ocular dominance plasticity (Wiesel and Hubel 1963). After the closure of one eye during a critical period of early postnatal life, the input from the open eye subsequently has a larger cortical territory than the input from the deprived eye. Critical period plasticity is best viewed as a continuum of local circuit computations that result in a structural rewiring of thalamic afferents (Hensch 2005).

The mechanism of visual cortical plasticity was analyzed in detail with regard to the contribution of intracortical

GABAergic transmission. GABAergic transmission was modulated locally by infusion of the benzodiazepine agonist diazepam or the inverse agonist DMCM. Following chronic infusion of diazepam into the striate cortex (starting at postnatal days 14–17), the spacing of the ocular columns was widened, whereas infusion of DMCM reduced the spacing (Hensch and Stryker 2004). Visual responsiveness remained undisturbed under these conditions (Hensch and Stryker 2004). Thus, intracortical GABA interneurons shape the geometry of the incoming thalamic arbours. In addition, the degree of GABAergic inhibition has been found to be a key determinant for the onset of critical period plasticity. The enhancement of GABA transmission by diazepam has long been known to induce the premature onset of the critical period (Fagiolini and Hensch 2000). It has now been found that only circuits containing α_1GABA$_A$ receptors drive cortical plasticity, whereas α_2-enriched connections separately regulate neuronal firing (Fagiolini et al. 2004). These results are based on the use of knock-in mice in which the respective individual α-subunit had been rendered diazepam-insensitive by a point mutation (Rudolph et al. 1999; Löw et al. 2000). These recent findings therefore present a cellular and molecular basis for critical period plasticity in the visual cortex triggered by neuronal inhibition (Fagiolini et al. 2004; Ferster 2004).

For ocular stripes to form postnatally, activity in nearby inputs from the same eye are considered to cooperate with each other as cluster of cortical cells in their bid to take over cortical territory (Ferster 2004). By lateral GABAergic inhibitory connections, activity in more distant cells must be “anti-correlated”. Inputs from the same eye are therefore suppressed in their bid to take over the adjacent territories. The pattern of ocular dominance columns thus arises during the segregation of eye-specific inputs to the visual cortex in a self-organizing process. The cortex itself, through a specific type of GABAergic interneuron, plays a central role in organizing this pattern (Ferster 2004). The special developmental function of neocortical α_1GABA$_A$ receptors suggests that constraints should be placed on drugs designated for use in human infants (Fagiolini et al. 2004).

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