Pathophysiological aspects of diversity in neuronal inhibition: a new benzodiazepine pharmacology

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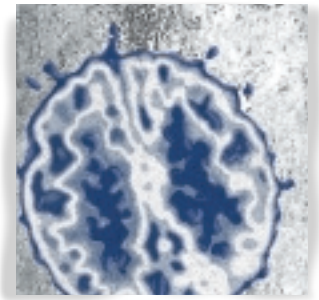

Inhibitory interneurons in the brain provide the balance to excitatory signaling. On the basis of brain imaging and human genetics, a deficit in GABAergic inhibition (GABA, γ-aminobutyric acid) has been identified as contributing to the pathophysiology of anxiety disorders, epilepsy, and schizophrenia. Therapeutically, $GABA_A$ receptors play a major role as targets for benzodiazepine drugs. The therapeutic relevance of the multitude of structurally diverse $GABA_A$ receptor subtypes has only recently been identified. α_1-$GABA_A$ receptors were found to mediate sedation, anterograde amnesia, and part of the seizure protection of these drugs, whereas α_2-$GABA_A$ receptors, but not α_3-$GABA_A$ receptors, mediate anxiolysis. Rational drug targeting to specific receptor subtypes has now become possible. Only restricted neuronal networks will be modulated by the upcoming subtype-selective drugs. For instance, anxiolytics devoid of drowsiness and sedation promise more sophisticated interventions in anxiety disorders. A new pharmacology of the benzodiazepine site is on the horizon.

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Inhibitory interneurons in brain function

In the harmonious brain, excitatory and inhibitory synaptic signals coexist in a purposeful balance. However, whereas the neurons that transmit excitatory signals often have rather stereotyped properties, the cells that signal inhibition in the cortex and hippocampus are highly diverse and strikingly different. Inhibitory cells—mostly interneurons because of their often short-range effect—signal to other neurons by liberating, in most cases, the neurotransmitter γ-aminobutyric acid (GABA). Most importantly, the interneurons are built for speed: their action potential is traditionally faster than that of pyramidal cells. Furthermore, the kinetics of synaptic events that excite inhibitory cells are faster than those that excite pyramidal cells.[1,2] The functional result is that pyramidal cell firing is under strict time control to prevent run-away excitation *(Figure 1)*. For instance, in feedforward inhibition, the bisynaptic inhibitory response arrives only 1 to 5 milliseconds after the monosynaptic excitatory input and thereby limits the time window for the summation of excitatory inputs to generate an action potential.[3] In addition to feedforward inhibition, there is feedback inhibition, the output-regulated breaking system for pyramidal cell firing. The firing of a pyramidal cell activates the inhibitory interneuron, which, in turn, inhibits the pyramidal cell. Once the feedback inhibition decays, the principal cell is able to fire again and initiates another cycle of inhibition. Thus,

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this type of inhibitory feedback circuit represents the most simple network for generating a neuronal oscillation *(Figure 1)*. Spontaneous activity in the nervous system often takes the form of rhythms of different frequencies, which underlines the functional relevance of inhibitory interneurons.[4]

Different patterns of rhythmic activity, including theta (4 to 12 Hz), gamma (30 to 100 Hz), and fast (>200 Hz) oscillations, which involve the synchronous firing of principal neurons and interneurons, subserve many functions in the developing and adult central nervous system (CNS). Cortical interneuron networks may generate both slow and fast cortical oscillatory activity.[5-10] Similarly, inhibitory neurons of the thalamic reticular and perigeniculate nuclei generate the synchronized activity of thalamocortical networks.[11] Gamma oscillations (30 to 100 Hz) occur in various brain structures[12,13] and can do so over large distances. They could, therefore, provide a substrate for "binding" together spatially separate areas of cortex, a hypothetical process whereby disparate aspects of a complex object, for example, are combined to form a unitary perception of it.[12,14]

Pathophysiology of neuronal inhibition

If the balance between excitatory and inhibitory activity is shifted pharmacologically in favor of GABA, then anxiolysis, sedation, amnesia, and ataxia arise. On the other hand, an attenuation of the GABAergic system results in arousal, anxiety, restlessness, insomnia, exaggerated reactivity, and even seizures. These pharmacological manifestations point to the contribution of inhibitory neurotransmission to the pathophysiology of brain disorders. A GABAergic deficit is particularly apparent in anxiety disorders, epilepsy, and schizophrenia.

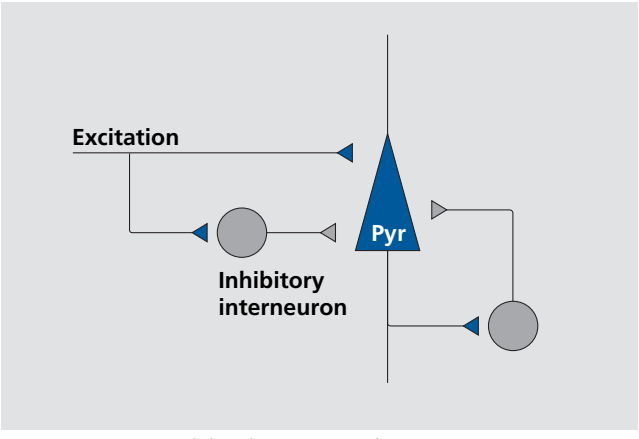

Figure 1. Scheme of feedforward and feedback inhibition through GABAergic interneurons. Pyr, pyramidal cell; GABA, γ-aminobutyric acid.

Anxiety disorders

Anxiety disorders have a high prevalence and are the most common cause of medical intervention in primary care.[15] The pharmacology of the GABA system supports the view that GABAergic dysfunctions are causally related to symptoms of anxiety. For instance, pentylenetetrazole acts by blocking $GABA_A$ receptor function and produces extreme anxiety, traumatic memories, and extreme avoidance behavior when used clinically.[16] Conversely, enhancing GABAergic transmission, eg, by benzodiazepines, is a powerful mechanism to inhibit the experience of anxiety and its aversive reinforcement.

Neuroimaging has given fresh insight into the role of GABAergic inhibition in anxiety disorders. In a recent positron emission tomography (PET) study using ^{11}C-flumazenil, a significant global reduction in flumazenil binding to $GABA_A$ receptors was apparent throughout the brain in patients with panic disorder *(Figure 2)*.[17] The greatest decrease observed occurred in areas thought to be involved in the experience of anxiety, such as the orbitofrontal and temporal cortex. Single photon emission computed tomography (SPECT) studies using the related radioligand ^{123}I-iomazenil have shown similar decreases in binding.[18] A localized reduction in benzodiazepine binding in the temporal lobe has also been reported in generalized anxiety disorders.[19] Furthermore, magnetic resonance spectroscopy has been used to show decreased cortical levels of GABA in patients with panic disorders.[20] These findings are consistent with the view that at least some anxiety disorders are linked to a defective GABAergic neuroinhibitory process.[21]

Anxiety in humans frequently arises at the interface between a genetic predisposition and experience. Recently, the hypothesis that a partial $GABA_A$ receptor deficit would be sufficient to generate an anxiety state was tested. Using molecular biological techniques, the $GABA_A$ receptor deficit seen in patients with anxiety disorders[17] was reproduced in an animal model.[22] The γ_2-subunit of the $GABA_A$ receptor is known to anchor the receptors in the subsynaptic membrane. By reducing the gene dosage for the γ_2-subunit in mice—heterozygosity for the γ_2-subunit gene—the synaptic clustering of

$GABA_A$ receptors was reduced. A partial receptor deficit was apparent throughout most of the brain including the areas that are known to be involved in the processing of anxiety responses, such as the cerebral cortex, amygdala, and hippocampus. The animals behaved normally in a wide range of behavioral tests except when exposed to aversive situations caused by either natural or conditioned fear stimuli. Under such conditions, enhanced anxiety responses and a bias for threat cues were observed.[22] The bias of the animals for threat cues was especially significant since this behavior corresponds to the cognitive deficit contributing to the inability of anxious individuals to distinguish an ambiguous from a threatening situation.[23] Thus, a $GABA_A$ receptor deficit is considered as a predisposition for anxiety disorders in humans. It appears that anxiety symptoms are a sensitive manifestation of an impaired GABAergic neurotransmission.[21,22,24]

Epilepsy

Modification of activity at GABAergic synapses powerfully influences epileptic phenomena. This is a consequence of the role of GABAergic synapses in recurrent inhibitory systems in cortical and other structures, and their effect in limiting the excessive discharge of principal neurons in time and space.

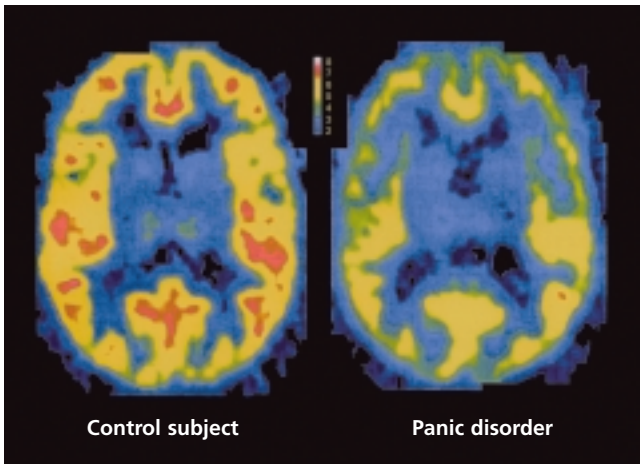

Figure 2. Panic anxiety. Compared with control subjects a reduction in $GABA_A$ receptor binding is apparent in panic disorder by positron emission tomography (PET) imaging with ^{11}C-flumazenil.[17] GABA, γ-aminobutyric acid.
Reproduced from reference 17: Malizia AL, Cunningham VJ, Bell CJ, Liddle PF, Jones T, Nutt DJ. Decreased brain $GABA_A$-benzodiazepine receptor binding in panic disorders: preliminary results from a quantitative PET study. *Arch Gen Psychiatry*. 1998;55:715-720. Copyright © 1998, American Medical Association.

Genetic evidence provided the most direct link of epilepsy to $GABA_A$ receptor dysfunction. A K289M mutation located in the extracellular loop of the γ_2-subunit between the transmembrane domain 2 and 3, was linked to familial generalized epilepsy with febrile seizures.[25] At recombinant $GABA_A$ receptors, the K289M mutation reduced the GABA-activated current. Another mutation in the γ_2 subunit of $GABA_A$ receptor was linked to childhood absence epilepsy and febrile seizures with a conserved arginine residue being mutated to glutamine (R43Q).[26] However, since childhood absence epilepsy is not inherited in a simple mendelian manner, the point mutation is not considered to be sufficient by itself to cause this phenotype.
Another example of an altered GABAergic function is that of generalized seizures in infancy related to a pyridoxine deficiency. Since pyridoxal phosphate is a cofactor of glutamic acid decarboxylase, the seizures are related to a deficient synthesis of GABA and can be treated by moderate or high doses of pyridoxine. Furthermore, multiple forms of epilepsy occur in the neurodevelopmental disorder, known as Angelman syndrome, which also shows mental retardation and facial dysmorphism. Genetic studies commonly reveal a major deletion on maternal chromosome 15q11-13[27] with two genes being the major contributors to the syndrome—one is *UBE3A*, encoding a ubiquitin ligase, the other is *GABRB3* encoding the β_2 subunit of $GABA_A$ receptor. Absence epilepsy in man, with a 2- to 3-Hz spike-and-wave discharge in the cortex, is dependent on a thalamocortical loop, which involves several sets of GABAergic synapses in cortex and thalamus. The "waves" correspond to hyperpolarizing activity resulting from synchronous firing of GABAergic neurons.[28] The effects of GABA-related drugs are however complex. Agonists at $GABA_B$ receptors, such as baclofen, exacerbate the spike-and-wave discharges in man and animals; $GABA_B$ antagonists suppress them. Compounds potentiating $GABA_A$ synaptic function commonly exacerbate the discharges, although some benzodiazepines with subtype selective actions can decrease the spike-and-wave discharges. Nevertheless, approximately half the antiepileptic drugs in clinical use are thought to owe their efficacy to either totally or partially potentiating GABAergic inhibitory effects.[29]

Schizophrenia

The neurobiology of schizophrenia has been dominated for the last 30 years by the dopamine hypothesis, although

other transmitter systems are also affected. Alterations in cortical GABAergic systems have been reported in postmortem brain of schizophrenic patients, such as reduced uptake and release of GABA and a reduced activity of glutamic acid decarboxylase. Most conspicuously, the density of axon terminals of GABAergic chandelier neurons was reduced by 40% in the prefrontal cortex.[30] By their axon terminals, chandelier neurons are positioned to powerfully regulate the excitatory output of pyramidal neurons and consequently affect the pattern of neuronal activity in the prefrontal cortex and its projection areas.[30] In addition, altered ratios of subunit splice variants of $GABA_A$ receptors were found in prefrontal cortex of schizophrenics.[31] In addition, benzodiazepine receptor inverse agonists are associated with psychotogenic effects.[32] Furthermore, in primate brain, D_4 dopamine receptors (a member of the D_2 dopamine receptor family with a high affinity for clozapine) modulate GABAergic interneurons in critical brain areas (cerebral cortex, hippocampus, thalamic reticular nucleus, and globus pallidus). Thus, the beneficial effects of clozapine in schizophrenia may be achieved, in part, through D_4-mediated GABA modulation.[33] Finally, GABAergic neurons have been found to be especially vulnerable to glucocorticoid hormones and to glutamatergic excitotoxicity, which may explain the increased number of certain glutamatergic neurons in, for example, the cingulate gyrus of schizophrenic brains and this, in conjunction with a postulated role of stress in the pathogenesis of schizophrenia, would strengthen the assumption of an important role for a GABAergic deficit in schizophrenia.[34] A GABAergic dysfunction that might arise in the course of the disorder may result in long-lasting and perhaps lifelong neuronal sensitivity changes.

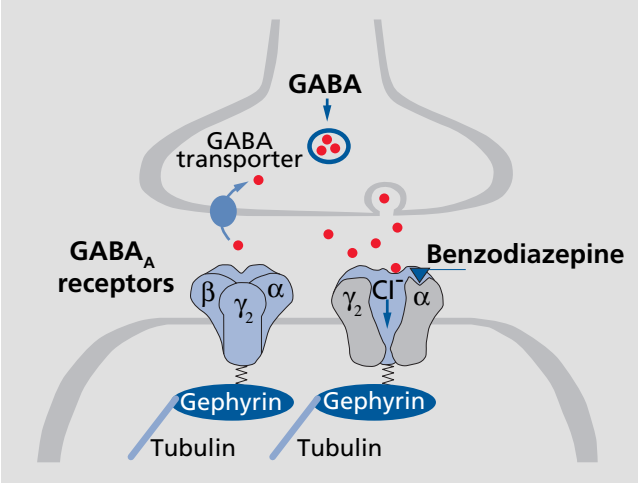

Figure 3. Scheme of a GABAergic synapse depicting the major elements of signal transduction. The ionotropic $GABA_A$ receptors are heteromeric membrane proteins linked in a yet unknown, indirect way to the synaptic anchoring protein gephyrin and the cytoskeleton. GABA, γ-aminobutyric acid.

Modified from reference 35: Möhler H, Fritschy JM, Rudolph U. A new benzodiazepine pharmacology. *J Pharmacol Exp Ther*. 2002;300:2-8. Copyright © 2002, American Society for Pharmacology and Experimental Therapeutics.

Pharmacology of the GABA system

$GABA_A$ receptors are prominent drug targets in that they mediate the action of barbiturates, anesthetics, and neurosteroids and, most importantly, represent the exclusive sites of actions of benzodiazepine drugs, which are in wide clinical use as anxiolytics, hypnotics, and anticonvulsants.[35]

Synaptic action of benzodiazepines

Benzodiazepine drugs modulate $GABA_A$ receptor function in a sophisticated manner that is use-dependent and synapse-specific *(Figure 3)*. Benzodiazepines only become effective at $GABA_A$ receptors that are activated by GABA. In the absence of GABA, the drug remains ineffective (use-dependency). The maximal drug effect varies with the operational configuration of the GABAergic synapse. The number of receptors or the concentration of GABA in the synaptic cleft can differ between synapses. If the release of a single quantum of GABA is able to saturate all the $GABA_A$ receptors, the GABA-induced peak response is not enhanced, or only minimally, in the presence of benzodiazepines. In a synapse that operates under nonsaturating conditions, the drug-induced increase in the affinity of the receptor for GABA results in the recruitment of more receptors for activation by GABA. Thus, benzodiazepine drugs become most strongly effective when the GABAergic operation of the synapse is submaximal.[36,37]

$GABA_A$ receptors and their multiplicity

On the basis of the presence of 7 subunit families comprising at least 18 subunits in the CNS (α_{1-6}, β_{1-3}, γ_{1-3}, δ, ε, θ, and ρ_{1-3}), the pentameric $GABA_A$ receptors display an extraordinary structural heterogeneity. Most $GABA_A$ receptors subtypes in vivo are believed to be composed of α, β, and γ subunits. The physiological significance of the structural diversity of $GABA_A$ receptors lies in the provision of receptors that differ in their channel kinetics, affinity for GABA, rate of desensitization, and subcellular positioning.[24]

For instance, synaptic and extrasynaptic $GABA_A$ receptors differ kinetically. Extrasynaptic $GABA_A$ receptors containing the δ subunit in dentate gyrus and cerebellum are tailor-made for tonic inhibition, due to their high affinity for GABA and slow desensitization kinetics.[38,39] Marked differences in desensitization kinetics have also been reported for synaptic and extrasynaptic receptors in inferior olivary neurons.[40] Further insights into the heterogeneity of $GABA_A$ receptors is expected to arise from the identification of receptor-associated proteins and their regulation.[41]

Diazepam-sensitive $GABA_A$ receptors

Functionally, $GABA_A$ receptors are best distinguished by their pharmacology. 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 benzodiazepine sensitive. These receptors represent about 90% of all $GABA_A$ receptors with the major receptor subtype being assembled from the subunits $\alpha_1\beta_2\gamma_2$. Only a few brain regions lack this receptor *(Table I)*.[42-44]

Receptors containing the α_2 or α_3 subunit are 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 ($\alpha_3\beta_3\gamma_2$) *(Table I)*.

Receptors containing the α_5 subunit are of minor abundance in the whole 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 *(Table I)*.

A new benzodiazepine pharmacology

In the search for benzodiazepine site ligands with higher therapeutic selectivity and a reduced side-effect profile, drugs acting at $GABA_A$ receptor subtypes have long been considered to be of potential benefit. However, it was only recently that the pharmacological relevance of $GABA_A$ receptor subtypes was identified based on a genetic approach.[45,46] Mouse lines were generated in which either the α_1-, α_2-, or α_3-$GABA_A$ receptor subtype was diazepam-insensitive. Thus, a deficit in the behavioral response to diazepam was an indication for the role of the respective receptor subtype in wild-type mice.[45,46] This strategy permitted the allocation of the benzodiazepine drug actions to identified $GABA_A$ receptor subtypes *(Figure 4)*.[36,47] In addition, it implicated the neuronal networks expressing the particular receptor in mediating the corresponding drug actions. Experimentally, the benzodiazepine sites were rendered diazepam-insensitive by replacing a conserved histidine residue with an arginine residue in the corresponding α subunit genes (α_1(H101R), α_2(H101R), α_3(H126R), and α_5(H105R)).[45,46]

Composition	Pharmacological characteristics
$\alpha_1\beta_2\gamma_2$	Major subtype (60% of all $GABA_A$ receptors). Mediates the sedative, amnestic, and—to a large extent—anticonvulsant action of benzodiazepine site agonists. High affinity for classical benzodiazepines, zolpidem, and the antagonist flumazenil.
$\alpha_2\beta_3\gamma_2$	Minor subtype (15% to 20%). Mediates anxiolytic action of benzodiazepine site agonists. High affinity for classical benzodiazepine agonists and the antagonist flumazenil. Intermediate affinity for zolpidem.
$\alpha_3\beta_n\gamma_2$	Minor subtype (10% to 15%). High affinity for classical benzodiazepine agonists and the antagonist flumazenil. Intermediate affinity for zolpidem.
$\alpha_4\beta_n\gamma$ / $\alpha_4\beta_n\delta$	Less than 5% of all receptors. Insensitive to classical benzodiazepine agonists and zolpidem.
$\alpha_5\beta_{1/3}\gamma_2$	Less than 5% of all receptors. High affinity for classical benzodiazepine agonists and the antagonist flumazenil. Very low affinity for zolpidem.
$\alpha_6\beta_{2,3}\gamma_2$ / $\alpha_6\beta_n\delta$	Less than 5% of all receptors. Insensitive to classical benzodiazepine agonists and zolpidem. Minor population. Lacks benzodiazepine site.
ρ	Homomeric receptors. Insensitive to bicuculline, barbiturates, baclofen, and all benzodiazepine site ligands. Also termed $GABA_C$ receptor. For nomenclature, see reference 44.

Table I. $GABA_A$ (γ-aminobutyric acid) receptor subtypes.
Modified from reference 35: Möhler H, Fritschy JM, Rudolph U. A new benzodiazepine pharmacology. *J Pharmacol Exp Ther*. 2002;300:2-8. Copyright © 2002, American Society for Pharmacology and Experimental Therapeutics.

Sedation

Sedation is a major property of many benzodiazepine site ligands and has now been shown to be mediated via $GABA_A$ receptors. Among α_1-, α_2-, and α_3-point-mutated mice only the α_1(H101R) mutants were resistant to the depression of motor activity by diazepam and zolpidem.[45,46,48] This effect was specific for ligands of the benzo-diazepine site since pentobarbital or a neurosteroid remained as effective in α_1(H101R) mice as in wild-type mice in inducing sedation. An α_1(H101R) mouse line was also generated by McKernan et al[49] confirming that sedation is linked to α_1-$GABA_A$ receptors.

Amnesia

Anterograde amnesia is a classical side effect of benzodiazepine drugs. The memory-impairing effect of diazepam, analyzed in a step-through passive avoidance paradigm, was strongly reduced in the α_1(H101R) mice compared with wild-type mice, as shown by the increased latency for reentering the dark compartment 24 hours after training.[45] This effect was not due to a potential nonspecific impairment, since the ability of a muscarinic antagonist to induce amnesia was retained in the α_1(H101R) mice. These results demonstrate that diazepam-induced anterograde amnesia is mediated by α_1-$GABA_A$ receptors.

Protection against seizures

The anticonvulsant activity of diazepam, assessed by its protection against pentyleneterazole-induced tonic convulsions, was reduced in α_1(H101R) mice compared with wild-type animals.[45] Sodium phenobarbital remained fully effective as anticonvulsant in α_1(H101R) mice.

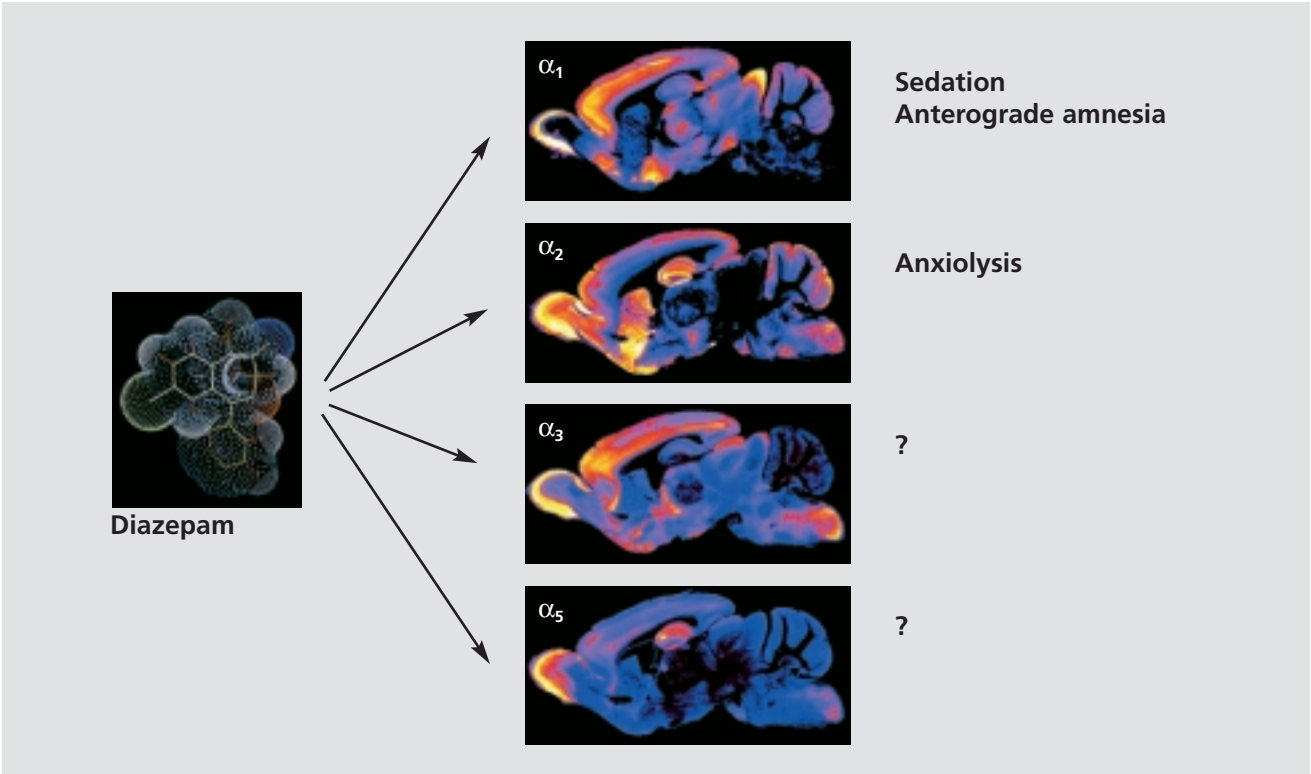

Figure 4. The four classes of diazepam-sensitive $GABA_A$ receptors are distinguished by the type of α-subunit (α_1, α_2, α_3, or α_5). Their largely distinct neuronal localizations are demonstrated immunohistochemically in mouse brain sections. The major known pharmacological actions mediated via the respective receptor subtypes are indicated. The α_5-$GABA_A$ receptors have recently been found to be involved in the formation of associative memory.[47]

Modified from reference 36: Rudolph U, Crestani F, Möhler H. $GABA_A$ receptor subtypes: dissecting their pharmacological functions. *Trends Pharmacol Sci*. 2001;22:188-194. Copyright © 2001, Elsevier Science Ltd.

These results show that the anticonvulsant activity of benzodiazepines is partially, but not fully mediated by α_1-GABA$_A$ receptors. The anticonvulsant action of zolpidem is exclusively mediated by α_1-GABA$_A$ receptors, since its anticonvulsant action is completely absent in α_1(H101R) mice.[48]

Anxiolysis

New strategies for the development of daytime anxiolytics that are devoid of drowsiness and sedation are of high priority. Experimentally, the anxiolytic-like activity of diazepam can be assessed by exposing wild-type animals to naturally aversive stimuli. For instance, in an elevated plus-maze test, the time spent on an open arm is enhanced after diazepam treatment, as is the time spent in the lit area of a light/dark choice test. In contrast, mice with a benzodiazepine-insensitive α_2-GABA$_A$ receptor (α_2(H101R)) were resistant to the effect of diazepam in these test paradigms.[46] Thus, the anxiolytic-like action of diazepam is attributed to the modulation of α_2-GABA$_A$ receptors. They are highly specific targets for the development of future selective anxiolytic drugs. The α_2-GABA$_A$ receptors, which comprise only about 15% of all diazepam-sensitive GABA$_A$ receptors, are mainly expressed in the amygdala and in principal cells of the cerebral cortex and the hippocampus with particularly high densities on their axon initial segments.[50,51] Thus, the inhibition of the output of these principal neurons appears to be a major mechanism of anxiolysis.

It had previously been assumed that the anxiolytic action of diazepam is based on the dampening of the reticular activating system. It is mainly represented by noradrenergic and serotonergic neurons of the brain stem, which express exclusively α_3-GABA$_A$ receptors. The analysis of the α_3-point-mutated mice (α_3(H126R)) indicated that the anxiolytic effect of benzodiazepine drugs, measured as described above, is not mediated by α_3-GABA$_A$ receptors.[46] The reticular activating system therefore does not appear to be a major contributor to anxiolysis. The role of α_3-GABA$_A$ receptors remains to be identified.

Myorelaxation

The muscle relaxant effect of diazepam is largely mediated by α_2-GABA$_A$ receptors, as shown by the failure of diazepam to induce changes in muscle tone in the α_2-point-mutated mouse line.[52] In addition to the areas described above, α_2-GABA$_A$ receptors are expressed in the spinal cord, notably in the superficial layer of the dorsal horn and in motor neurons,[53] the latter being most likely implicated in muscle relaxation. It is important to note that the muscle relaxant effect requires considerably higher doses of diazepam than its anxiolytic-like activity, which is mediated by α_2-GABA$_A$ receptors located in the limbic system (see above). Thus, a higher receptor occupancy seems to be required for muscle relaxation compared with the anxiolytic-like action of diazepam. It was only at very high doses of diazepam that α_3-GABA$_A$ receptors were also implicated in mediating myorelaxation.[52] ❑

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Aspectos fisiopatológicos de la diversidad en la inhibición neuronal: una nueva farmacología benzodiazepínica

Las interneuronas inhibitorias en el cerebro permiten equilibrar las señales excitatorias. En base a los estudios de neuroimágenes y de genética humana se ha identificado que un déficit de la inhibición gabaérgica (ácido gama amino butírico) contribuye a la fisiopatología de los trastornos de ansiedad, la epilepsia y la esquizofrenia. Los receptores $GABA_A$ juegan un rol principal como blancos para la acción terapéutica de las drogas benzodiazepínicas. Sólo recientemente ha sido identificada la importancia terapéutica de un sinnúmero de subtipos, estructuralmente diversos, del receptor $GABA_A$. Se encontró que los receptores $GABA_A\alpha_1$ mediaban la sedación, la amnesia anterógrada y parte de la protección contra las convulsiones de estas drogas, mientras que los receptores $GABA_A\alpha_2$, pero no los receptores $GABA_A\alpha_3$, mediaban la ansiolisis. Actualmente ha llegado a ser posible contar con drogas dirigidas racionalmente contra subtipos específicos del receptor. Sólo redes neuronales restringidas serán moduladas por la aparición de drogas subtipo selectivas. Por ejemplo, ansiolíticos exentos de somnolencia y sedación prometen intervenciones más sofisticadas para los trastornos de ansiedad. En el horizonte se cuenta con una nueva farmacología del sitio benzodiazepínico.

Aspects physiopathologiques de la diversité dans l'inhibition neuronale : une nouvelle pharmacologie des benzodiazépines

Les interneurones inhibiteurs du cerveau assurent l'équilibre des signaux de l'excitation. L'imagerie cérébrale et la génétique humaine ont montré qu'un déficit dans l'inhibition GABAergique (GABA, acide γ-aminobutyrique) contribuait à la physiopathologie de l'anxiété, de l'épilepsie et de la schizophrénie. Sur le plan thérapeutique, les récepteurs $GABA_A$ jouent un rôle majeur en tant que cible des benzodiazépines. Ce n'est que récemment que l'importance thérapeutique de la multitude des sous-types de récepteurs $GABA_A$ a été reconnue. Les récepteurs α_1-$GABA_A$ sont des médiateurs dans la sédation, l'amnésie antérograde et participent à l'activité protectrice des benzodiazépines dans la crise d'épilepsie, alors que les récepteurs α_2-$GABA_A$ - mais pas les récepteurs α_3-$GABA_A$ - sont des médiateurs de l'anxiolyse. Il est désormais possible d'utiliser de façon ciblée les molécules spécifiques des divers sous-types de récepteurs. Les prochains médicaments sélectifs pour les sous-types de récepteurs ne moduleront que des réseaux neuronaux limités. C'est ainsi que des anxiolytiques dénués d'effets sédatifs ou de somnolence permettront une efficacité plus marquée dans les troubles anxieux. Une nouvelle pharmacologie des sites benzodiazépiniques pointe à l'horizon.

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