Basic research

Pathophysiological aspects of diversity in neuronal inhibition: a new benzodiazepine pharmacology
Hanns Möhler, PhD

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 braking 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,

Keywords: GABA (γ-aminobutyric acid); GABAA receptor; neuronal inhibition; anxiety; epilepsy; schizophrenia; benzodiazepine

Author affiliations: Institute of Pharmacology and Toxicology, University of Zurich and Department of Applied Biosciences, Federal Institute of Technology (ETH) Zurich, Zurich, Switzerland

Address for correspondence: Prof H. Möhler, Institute of Pharmacology and Toxicology, University of Zurich and Department of Applied Biosciences, Federal Institute of Technology (ETH) Zurich, Winterthurerstr 190, CH-8057 Zurich, Switzerland (e-mail: mohler@pharma.unizh.ch)
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.5

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,7-10 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 structures12,13 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.

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 11C-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 123I-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 disorders17 was reproduced in an animal model.22 The γ2-subunit of the GABA_A receptor is known to anchor the receptors in the subsynaptic membrane. By reducing the gene dosage for the γ2-subunit in mice—heterozygosity for the γ2-subunit gene—the synaptic clustering of
GABA<sub>A</sub> 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. 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. Thus, a GABA<sub>A</sub> 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.

**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.

Genetic evidence provided the most direct link of epilepsy to GABA<sub>A</sub> receptor dysfunction. A K289M mutation located in the extracellular loop of the γ<sub>2</sub>-subunit between the transmembrane domain 2 and 3, was linked to familial generalized epilepsy with febrile seizures. At recombinant GABA<sub>A</sub> receptors, the K289M mutation reduced the GABA-activated current. Another mutation in the γ<sub>2</sub> subunit of GABA<sub>A</sub> receptor was linked to childhood absence epilepsy and febrile seizures with a conserved arginine residue being mutated to glutamine (R43Q). 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 with two genes being the major contributors to the syndrome—one is <i>UBE3A</i>, encoding a ubiquitin ligase, the other is <i>GABRB3</i> encoding the β<sub>2</sub> subunit of GABA<sub>A</sub> receptor. Absence epilepsy in man, with a 2- to 3-Hz spike-and-wave discharge in the cortex, is dependent on a thalamo-cortical 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. The effects of GABA-related drugs are however complex. Agonists at GABA<sub>B</sub> receptors, such as bacetofen, exacerbate the spike-and-wave discharges in man and animals; GABA<sub>B</sub> antagonists suppress them. Compounds potentiating GABA<sub>A</sub> 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.

**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 glutamic acid decarboxylase. Most conspicuously, the density of axon terminals of GABAergic chandelier neurons was reduced by 40% in the prefrontal cortex. 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. 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.

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 (α₁-α₆, β₁-β₃, γ₁-γ₃, δ, ε, θ, and ρ₁-ρ₃), 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.39
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. Marked differences in desensitization kinetics have also been reported for synaptic and extrasynaptic receptors in inferior olivary neurons. Further insights into the heterogeneity of GABA_A receptors is expected to arise from the identification of receptor-associated proteins and their regulation.

**Diazepam-sensitive GABA_A receptors**

Functionally, GABA_A receptors are best distinguished by their pharmacology. Receptors containing the α₁, α₂, α₃, or α₅ subunits in combination with any of the β subunits and the γ₂ subunit are benzodiazepine sensitive. These receptors represent about 90% of all GABA_A receptors with the major receptor subtype being assembled from the subunits α₁β₂γ₂. Only a few brain regions lack this receptor (Table I).

Receptors containing the α₂ or α₃ subunit are less abundant and are highly expressed in brain areas where the α₁ subunit is absent or present at low levels. The α₂ and α₃ subunits are frequently coexpressed with the β₁ and γ₂ subunits, which is particularly evident in hippocampal pyramidal neurons (α₂β₁γ₂) and in cholinergic neurons of the basal forebrain (α₃β₁γ₂) (Table I).

Receptors containing the α₅ 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 β₁ and γ₂ 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. Mouse lines were generated in which either the α₁-, α₂-, or α₅-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. This strategy permitted the allocation of the benzodiazepine drug actions to identified GABA_A receptor subtypes (Figure 4). 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 (α₁(H101R), α₂(H101R), α₃(H126R), and α₅(H105R)).

### Table I. GABA_A (γ-aminobutyric acid) receptor subtypes.

| Composition | Pharmacological characteristics |
|-------------|---------------------------------|
| α₁β₂γ₂ | 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. |
| α₁β₁γ₂ | Minor subtype (15% to 20%). Mediates anxiolytic action of benzodiazepine site agonists. High affinity for classical benzodiazepines and the antagonist flumazenil. |
| α₁β₅γ₂ | Minor subtype (10% to 15%). High affinity for classical benzodiazepine agonists and the antagonist flumazenil. Intermediate affinity for zolpidem. |
| α₁β₆γ₂ | Minor subtype (10% to 15%). High affinity for classical benzodiazepine agonists and the antagonist flumazenil. Intermediate affinity for zolpidem. |
| α₂β₃γ₂ / α₅β₃δ | Less than 5% of all receptors. Insensitive to classical benzodiazepine agonists and zolpidem. |
| α₁β₉α₁γ₂ | Less than 5% of all receptors. High affinity for classical benzodiazepine agonists and the antagonist flumazenil. Very low affinity for zolpidem. |
| α₂β₃γ₂ / α₅β₃δ | 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_A receptor. For nomenclature, see reference 44. |

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<sub>A</sub> receptors. Among α<sub>1</sub>-, α<sub>2</sub>-, and α<sub>3</sub>-point-mutated mice only the α<sub>3</sub>(H101R) mutants were resistant to the depression of motor activity by diazepam and zolpidem.<sup>45,46,48</sup> This effect was specific for ligands of the benzo-diazepine site since pentobarbital or a neurosteroid remained as effective in α<sub>1</sub>(H101R) mice as in wild-type mice in inducing sedation. An α<sub>1</sub>(H101R) mouse line was also generated by McKernan et al<sup>49</sup> confirming that sedation is linked to α<sub>1</sub>-GABA<sub>A</sub> 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<sub>1</sub>(H101R) mice compared with wild-type mice, as shown by the increased latency for reentering the dark compartment 24 hours after training.<sup>45</sup> 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<sub>1</sub>(H101R) mice. These results demonstrate that diazepam-induced anterograde amnesia is mediated by α<sub>1</sub>-GABA<sub>A</sub> receptors.

Protection against seizures

The anticonvulsant activity of diazepam, assessed by its protection against pentylentetrazole-induced tonic convulsions, was reduced in α<sub>1</sub>(H101R) mice compared with wild-type animals.<sup>45</sup> Sodium phenobarbital remained fully effective as anticonvulsant in α<sub>1</sub>(H101R) mice.

Figure 4. The four classes of diazepam-sensitive GABA<sub>A</sub> receptors are distinguished by the type of α-subunit (α<sub>1</sub>, α<sub>2</sub>, α<sub>3</sub>, or α<sub>5</sub>). 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<sub>3</sub>-GABA<sub>A</sub> receptors have recently been found to be involved in the formation of associative memory.<sup>47</sup>

Modified from reference 36: Rudolph U, Crestani F, Möhler H. GABA<sub>A</sub> 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 \( \alpha_1 \)-GABA\(_A\) receptors. The anticonvulsant action of zolpidem is exclusively mediated by \( \alpha_1 \)-GABA\(_A\) receptors, since its anticonvulsant action is completely absent in \( \alpha_1 \) (H101R) mice.\(^{46}\)

**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 \( \alpha_2 \)-GABA\(_A\) receptor (\( \alpha_2 \) (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 \( \alpha_2 \)-GABA\(_A\) receptors. They are highly specific targets for the development of future selective anxiolytic drugs. The \( \alpha_2 \)-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.\(^{3,51}\) 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 serotoninergic neurons of the brain stem, which express exclusively \( \alpha_2 \)-GABA\(_A\) receptors. The analysis of the \( \alpha_3 \)-point-mutated mice (\( \alpha_3 \) (H126R)) indicated that the anxiolytic effect of benzodiazepine drugs, measured as described above, is not mediated by \( \alpha_2 \)-GABA\(_A\) receptors.\(^{46}\) The reticular activating system therefore does not appear to be a major contributor to anxiolysis. The role of \( \alpha_3 \)-GABA\(_A\) receptors remains to be identified.

**Myorelaxation**

The muscle relaxant effect of diazepam is largely mediated by \( \alpha_2 \)-GABA\(_A\) receptors, as shown by the failure of diazepam to induce changes in muscle tone in the \( \alpha_2 \)-point-mutated mouse line.\(^{52}\) In addition to the areas described above, \( \alpha_2 \)-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 \( \alpha_2 \)-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 \( \alpha_3 \)-GABA\(_A\) receptors were also implicated in mediating myorelaxation.\(^{53}\) 

I thank my colleagues D. Benke, F Crespini, J. M. Fritschy, B. Linscher, and U. Rudolph for their great contributions.

**REFERENCES**

1. Martina M, Schultz JH, Ehmke H, Monyer H, Jonas P. Functional and molecular differences between voltage-gated K+ channels of fast-spiking interneurons and pyramidal neurons of rat hippocampus. J Neurosci. 1998;18:8111-8125.

2. Geiger JR, Lubke J, Roth A, Frotscher M, Jonas P. Submillisecond AMPA receptor-mediated signalling at a principal neuron-interneuron synapse. Neuron. 1997;18:1009-1023.

3. Scanziani M. GABA spillover activates postsynaptic GABA(B) receptors to control rhythmic hippocampal activity. Neuron. 2000;25:673-681.

4. Alger BE, Le Beau FEN. Physiology of the GABA and glycine systems In: Möhler H, ed. Pharmacology of GABA and Glycine Neurotransmission. New York, NY: Springer; 2001:3-76.

5. Whittington MA, Traub RD, Faulkner HJ, et al. Synchronized oscillations in interneuron network driven by metabotropic glutamate receptor activation. Nature. 1995;373:612-615.

6. Whittington MA, Traub RD, Faulkner HJ, et al. Recurrent excitatory postsynaptic potentials induced by synchronized fast cortical oscillations. Proc Natl Acad Sci U S A. 1997;94:12198-12203.

7. Buhl EH, Tamas G, Fisahn A. Cholinergic activation and tonic excitation induce persistent gamma oscillations in mouse somatosensory cortex in vitro. J Physiol (Lond). 1998;513:117-126.

8. Fisahn A, Pike FG, Buhl EH, et al. Cholinergic induction of network oscillations at 40 Hz in the hippocampus in vitro. Nature. 1998;394:186-189.

9. Penttonen M. Gamma frequency oscillation in the hippocampus of the rat: intracellular analysis in vivo. Eur J Neurosci. 1998;10:718-728.

10. Zhang Y, Perez Velazquez JL, Tian GF, et al. Slow oscillations (≤1 Hz) mediated by GABAergic interneuronal networks in rat hippocampus. J Neurosci. 1998;18:9256-9268.

11. McCormick DA, Bal T. Sleep and arousal: thalamocortical mechanisms. Ann Rev Neurosci. 1997;20:185-215.

12. Singer W, Gray CM. Visual feature integration and the temporal correlation hypothesis. Ann Rev Neurosci. 1995;18:555-586.

13. Laurent G. Dynamical representation of odors by oscillating and evolving neural assemblies. Trends Neurosci. 1996;19:489-496.

14. Traub RD, Whittington MA, Stanford IM, et al. A mechanism for generation of long-range synchronous fast oscillations in the cortex. Nature. 1996;38:621-624.
Aspects 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 en 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 benzdiazepínico.

Aspectos fisiopatológicos de la diversidad en la inhibición neuronal: una nueva 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.

---

15. Weiller E, Bisserbe JC, Maier W, Lecrubier Y. Prevalence and recognition of anxiety syndromes in five European primary care settings. A report from the WHO study on Psychological Problems in General Health Care. Br J Psychiatry Suppl. 1998;173:18-23.
16. Kaluff A, Nutt DJ. Role of GABA in memory and anxiety. Depress Anxiety. 1997;4:100-110.
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.
18. Malizia AL. What do brain imaging studies tell us about anxiety disorders? J Psychopharmacol. 1999;13:372-378.
19. Tiitinen J, Kuikka J, Rasenén P, et al. Cerebral benzodiazepine receptor binding and distribution in generalized anxiety disorders: a fractal analysis. Mol Psychiatry. 1997;2:463-471.
20. Goddard AW, Mason GF, Almai A, et al. Reductions in occipital cortex GABA levels in panic disorder detected 'H MRS. Arch Gen Psychiatry. 2001;58:556-561.
21. Nutt DJ, Malizia AL. New insights into the role of the GABA\(_A\) receptor in psychiatric disorders. Br J Psychiatry. 2001;179:390-396.
22. Crestani F, Lorez M, Baer K, et al. Decreased GABA\(_A\) receptor clustering results in enhanced anxiety and a bias for threat cues. Nat Neurosci. 1999;2:833-839.
23. Eysenck MW. The nature of anxiety In: Gale A, Eysenck MW, eds. Handbook of Individual Differences: Biological Perspectives. New York, NY: Wiley; 1992:157-178.
24. Möhler H. Functions of GABA receptors: pharmacology and pathophysiology In: Möhler H, ed. Pharmacology of GABA and Glycine Neurotransmission. New York, NY: Springer Publishers; 2001:101-116.
25. Baulac S, Huberfeld G, Gourfinkel-An I, et al. First genetic evidence of GABA\(_A\) receptor dysfunction in epilepsy: a mutation in the γ2-subunit gene. Nat Genet. 2001;28:46-48.
26. Wallace RH, Marini C, Petrou S, et al. Mutant GABA\(_A\) receptor γ2-subunit in childhood absence epilepsy and febrile seizures. Nat Genet. 2001;28:49-52.
27. Minassian BA, DeLorey TM, Olsen RW, et al. Angelman syndrome: correlations between epilepsy phenotypes and enotypes. Ann Neurol. 1998;43:485-493.
28. Snead OC 3rd, Depaulis A, Vergnes M, Marescaux C. Absence epilepsy: advances in experimental animal models. Adv Neurol. 1999;79:253-278.
29. Meldrum BS, Whiting P. Anticonvulsants acting on the GABA system. In: Möhler H, ed. Pharmacology of GABA and Glycine Neurotransmission. New York, NY: Springer; 2001:173-194.
30. Woo TU, Whitehead RE, Melchitzky DS, et al. A subclass of prefrontal GABA axon terminals are selectively altered in schizophrenia. Proc Natl Acad Sci U S A. 1998;95:5341-5346.
31. Huntsman MM, Tran BV, Potkin SG, et al. Altered ratios of alternatively spliced γ2 subunit of mRNAs of GABA_A receptors in prefrontal cortex of schizophrenics. Proc Natl Acad Sci U S A. 1998;95:15066-15071.
32. Sarter M, Bruno JP, Berntson GG. Psychotogenic properties of benzodiazepine receptor inverse agonists. Psychopharmacology. 2001;156:1-13.
33. Mrzljak L, Bergson C, Pappy M, et al. Localization of D4 receptors in GABAergic neurons in primate brain. Nature. 1996;381:245-248.
34. Carlsson A, Waters N, Holm-Waters S, et al. Interactions between monoamines, glutamate, and GABA in schizophrenia: new evidence. Ann Rev Pharmacol Toxicol. 2001;41:237-260.
35. Möhler H, Fritschy JM, Rudolph U. A new benzodiazepine pharmacology. J Pharmacol Exp Ther. 2002;300:2-8.
36. Rudolph U, Crestani F, Möhler H. GABA_A receptor subtypes: dissecting their pharmacological functions. Trends Pharmacol Sci. 2001;22:188-194.
37. Möhler H, Crestani F, Rudolph U. GABA_A-receptor subtypes: a new pharmacology. Curr Opin Pharmacol. 2001;1:22-25.
38. Brickley SG, Cull-Candy SG, Farrant M. Development of a tonic form of synaptic inhibition in rat cerebellar granule cells resulting from persistent activation of GABA_A receptors. J Physiol (Lond). 1996;497:753-759.
39. Mody I, Nusser Z. Differential activation of synaptic and extrasynaptic GABA_A receptors. Eur J Neurosci. 2000;11(suppl 12):398.
40. Devor A, Fritschy JM, Yarom Y. Synchronized and extrasynaptic GABA_A receptors in the inferior olivary nucleus differ in their spatial distribution, desensitization kinetics and subunit composition. J Neurophysiol. 2001;85:1686-1696.
41. Moss SJ, Smart TG. Constructing inhibitory synapses. Nat Rev Neurosci. 2001;2:240-250.
42. Fritschy JM, Möhler H. GABA_A receptor heterogeneity in the adult rat brain: differential regional and cellular distribution of seven major subunits. J Comp Neurol. 1995;359:154-194.
43. Pirker S, Schwarzer C, Wiesethaler A, Sieghart W, Sperk G. GABA_A receptors immunocytochemical distribution of 13 subunits in the adult rat brain. Neuroscience. 2000;101:815-850.
44. Barnard EA, Skolnick P, Olsen RW, et al. Subtypes of γ-aminobutyric acid_A receptors: classification on the bases of subunit structure and receptor function. Pharmacol Rev. 1998;50:291-313.
45. Rudolph U, Crestani F, Benke D, et al. Benzodiazepine actions mediated by specific γ-aminobutyric acid_A, receptor subtypes. Nature. 1999;401:796-800.
46. Löw K, Crestani F, Keist R, et al. Molecular and neuronal substrate for the selective attenuation of anxiety. Science. 2000;290:131-134.
47. Crestani F, Keist R, Fritschy JM, et al. Trace fear conditioning involves hippocampal α5 GABA_A receptors. Proc Natl Acad Sci U S A. 2002;99:8980-8985.
48. Crestani F, Martin JR, Möhler H, et al. Mechanism of action of the hypnotic zolpidem in vivo. Br J Pharmacol. 2000;131:1251-1256.
49. McKernan RM, Rosahl TW, Reynolds DS, et al. Sedative but not anxiolytic properties of benzodiazepines are mediated by the GABA_A receptor α1 subtype. Nat Neurosci. 2000;3:587-592.
50. Nusser Z, Sieghart W, Benke D, et al. Differential synaptic localization of two major γ-aminobutyric acid_A type α receptors on hippocampal pyramidal cells. Proc Natl Acad Sci U S A. 1996;93:11939-11944.
51. Fritschy JM, Johnson DK, Mohler H, et al. Independent assembly and subcellular targeting of GABA_A receptor subtypes demonstrated in mouse hippocampal and olfactory neurons in vivo. Neurosci Lett. 1998;249:99-102.
52. Crestani F, Löw K, Keist R, et al. Molecular targets for the myorelaxant action of diazepam. Mol Pharmacol. 2001;59:442-445.
53. Bohlhalter S, Weinmann O, Möhler H, et al. Laminar compartmentalization of GABA_A receptor subtypes in the spinal cord: an immunohistochemical study. J Neurosci. 1996;16:283-297.