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Pharmacology of the Benzodiazepine Receptor

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Summary. The benzodiazepine receptor (BZR) is an intrinsic allosteric modulatory site of the $GABA_A$-receptor-chloride channel complex of neuronal membranes mediating the main action of the major inhibitory neurotransmitter GABA. The BZR is unique in recognizing three classes of ligands, two of them producing opposite modulatory effects on the $GABA_A$ receptor function in an allosteric fashion (agonists and inverse agonists) and the third acting as antagonists of the two others. Agonists and partial agonists of the BZR (belonging to various chemical classes) have therapeutic applications as broad-spectrum tranquilizers and specific anxiolytics- anticonvulsants, respectively. The BZR antagonist flumazenil, recently introduced in therapy, increases the versatility of agonists in therapy and greatly simplifies the treatment of agonist overdosing. Inverse agonists are interesting probes to analyse the biological basis of anxiety-related emotional disorders.

Key words: Benzodiazepine receptor – $GABA_A$-receptor – Anxiolytics – Anxiogenics

Receptors and Channels

The central nervous system (CNS) is a large organ whose innumerable specific cellular elements, the neurones, arranged in enormously complex, intermingled networks, serve one major purpose, namely to communicate continuously with each other. This cross-talk determines the electrical activity of the individual neurones which process and integrate incoming information, physical and psychic needs, emotional states and mental processes to automatic and intentional somatic and mental outputs, to retrieve old information, and to add new data to the already existing stores. This interactive function of neurones is based on the numerous chemical signal substances, neurotransmitters and neuromodulators, as well as on the specific sets of ion channels and ion pumps in the membrane which determine the electrical firing patterns characteristic of individual neurones.

Accordingly, chemical agents which affect the activity of the CNS, in particular drugs, can do this by interfering with the interneuronal signalling systems or by interacting with the devices of the neuronal membrane that control ion transport into and out of the cell. Drug effects on intercellular signal systems (Table 1) of the (adult) CNS are mediated almost exclusively by their interaction with proteins of the phenotypic mechanisms subserving chemical signal production, release, recognition and transduction. Theoretically, chemical agents might also directly affect the transcription from coding genes, the translation and post-translational processing and intracellular transport of the various elements of these mechanisms. However, little is known to date about such effects of currently used drugs.

Interference with the *interneuronal signalling systems* is usually thought to be the most specific means of affecting CNS activity, a view which calls for a cautionary note. Indeed, while centrally active agents are known that interact virtually exclusively with one element of the signal systems at reasonable concentrations [the benzodiazepines (BZs), the topic of this presentation, are an excellent example], this specificity concerns a mechanism or site of action. It is a widely held illusion that altering the function of a distinct transmitter or modulator will result in a selective alteration of one distinct CNS function. The reasons

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Table 1. Major mechanisms by which drugs can produce useful changes in CNS activity

I. Interaction with interneuronal signal systems
Biosynthesis (enzymes, precursors)
Storage
Release (e.g. modulation by nerve terminal receptors)
Inactivation (cellular uptake, enzymatic degradation)
Receptors (signal binding sites, allosteric modulatory sites)
Post-receptor mechanisms (transduction mechanisms, second and third messengers)
II. Interaction with ion transport and permeation through neuronal membranes
Ion pumps
Ionophores
Fixed channels (K^+)
Voltage (potential)-operated channels (Na^+, K^+, Ca^{2+})
Receptor-operated channels (Na^+, K^+, Ca^{2+}, Cl^-)
Receptor-modulated voltage-operated channels (K^+)
Channels operated or modulated by intracellular messengers, such as ions, cyclic nucleotides, protein kinases (K^+)

why this is not so are, on the one hand, that no transmitter or neuromodulator mediates or alters one single CNS function but is involved in several or many functions and, on the other hand, that altering one of the signal systems will inevitably affect many other systems because of their complex interdependence.

The second major possible way of affecting CNS activity is by interacting with *transmembrane ion transport and permeation.* An increasing number of membrane ion channels are being discovered that differ in ion selectivity, conductance, gating mechanisms (voltage-, receptor-, ion-, intracellular messenger-dependent), activation and inactivation kinetics, localization and density on the neuronal surface. Individual neurones differ markedly, in part, by their sets of ion channels and, accordingly, by the characteristic patterns of electrical activity (frequency, rhythmicity, adaptation and facilitation, paroxysmal activity etc.) for which this set allows. Agents interacting exclusively with individual types of channels should affect only particular types of neuronal activity of particular types of neurones and, thereby, should allow for similarly or even more specific alterations of CNS functions as agents selective for individual signal systems. As an example of such agents, carbamazepine, which rather selectively affects in a voltage- and use-dependent manner the activity of sodium and calcium channels, has negligible effects on the normal CNS, highly effectively reduces some types of epileptic activity, and appears to be useful in certain psychic disorders.

Ligands of the benzodiazepine receptor (BZR), in particular the classic BZs, are among the most specific centrally active drugs with respect to site and mechanism of action. They interact with signal recognition and transduction by one type of receptor for the neurotransmitter γ-amino-butyric acid (GABA), the $GABA_A$ receptor. This interaction is through an allosteric modulatory site on the $GABA_A$ receptor. Allosteric modulation of a receptor function is a recently identified mechanism of drug action and the BZR is the presently most closely investigated example displaying, moreover, a particular complexity.

The GABAergic System

GABA is estimated to be used in approximately one-third of all synapses of the brain. It is the most abundant and important inhibitory neurotransmitter. Most GABAergic neurones are interneurones, present in all regions of the CNS, though in varying numbers. A few GABAergic neurones are principal output neurones with long axons projecting to distant regions, e.g. the Purkinje neurones of the cerebellar cortex, the strio-nigral and the nigro-thalamic and nigro-tectal neurones. GABA released from the endings of GABAergic neurones interacts with at least two different types of receptors. The most abundant and important type is the $GABA_A$ receptor, which is located on the membrane of the soma and dendrites of target neurones, as well as on the membrane of terminals of primary sensory neurones. $GABA_B$ receptors have a different distribution from $GABA_A$ receptors and seem to be present as autoreceptors on GABAergic cell bodies and nerve terminals. The characteristics of these two receptor types are shown in Table 2. Only the $GABA_A$ receptor will be considered here because BZs do not interact with the other type.

Table 2. Characteristics of the two presently known GABA receptors

	$GABA_A$ receptors	$GABA_B$ receptors
Common agonist	GABA	GABA
Selective agonist	Muscimol	Baclofen
Selective antagonist	Bicucculline	(δ-Amino-valeric acid)
Effector	Cl^- channel	Ca^{2+} channel ↓ AC ↓ K^+ channel ↑
Allosteric modulation	"Benzodiazepines", barbiturates, some convulsants	?

The $GABA_A$ receptor, as will be shown later in more detail, is part of a membrane chloride channel. Occupation of the receptor by GABA leads to the opening of the chloride channel, resulting in a chloride conductance of the membrane and a chloride flux mostly into the neurone, but sometimes also out of the cell, depending on the chloride concentration gradient across the membrane and the actual membrane potential. The GABA-induced chloride conductance can, therefore, lead to hyperpolarization, depolarization, or no change in the membrane potential. In all cases, however, it reduces neuronal excitability, by impeding the membrane from reaching the critical depolarization threshold for the generation of an action potential or by slowing down or blocking action potential propagation by short-circuiting the rapid sodium influx that underlies the action potential upstroke. These are the events which underlie the synaptic inhibitory action of GABA at the subsynaptic membrane.

The inhibitory function of GABAergic neurones within the neuronal networks of the CNS is illustrated schematically in Fig. 1, which shows, greatly simplified, the four principal circuits in which GABAergic neurones operate. Three circuits represent the so-called *postsynaptic type of inhibition,* where GABAergic neurones form synapses with the soma or dendrites of principal neurones, reducing the excitability of this neurone to all incoming excitatory signals. *Forward inhibition* means that the inhibitory command runs "parallel" to the excitation of the principal neurone. *Feedback inhibition* is the inhibition induced by the excitatory activity of the principal neurone itself. This type of circuit is regularly present in major output areas, such as around pyramidal cells in the cerebral cortex and the hippocampus and obviously serves to dampen the discharge frequency of these output neurones, which often tend to be triggered to high repetitive activity by even weak excitation when the "collateral" or "recurrent" inhibitory pathway fails. One synaptic arrangement in Fig. 1 produces the so-called *presynaptic type of inhibition.* In this case, the GABAergic interneurone forms axo-axonal synapses at the endings of an excitatory primary sensory neurone. GABA released at these terminal synapses reduces the release of the excitatory transmitter from the primary sensory neurone, thus inhibiting the excitation of the principal neurone by suppressing some of its inputs – however, without altering its excitability towards other inputs. The vital function of GABAergic synaptic inhibition is easily demonstrated by procedures that reduce its effectiveness, e.g. by blocking GABA receptors; excitation, anxiety, convulsions and death result from even a partial, generalized decrease of GABAergic function, and localized elimination of GABAergic mechanisms is a simple means of producing a focus of uncontrolled, epileptiform neuronal activity.

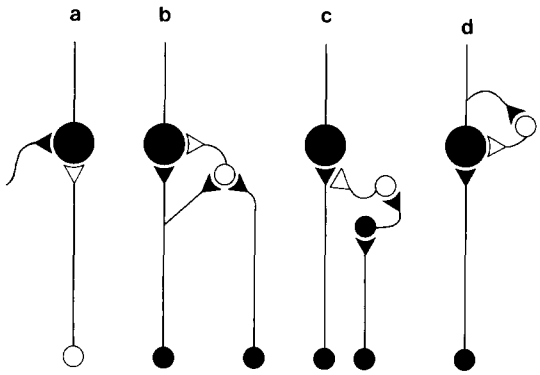

Fig. 1. Some prototype circuits containing GABAergic neurones *(open symbols).* Excitatory neurones are indicated by *filled symbols*

Benzodiazepine Tranquilizers and GABA

In 1975 two groups of researchers proposed that the classic BZs produced their effects by enhancing GABAergic synaptic transmission (Haefely et al. 1975; Costa et al. 1975). This view has since then been confirmed in numerous studies. Facilitation of GABAergic synaptic transmission by BZs has been found in all CNS areas investigated where GABA acts through $GABA_A$ receptors (Haefely and Polc 1986). Most illustrative are studies of the effect of BZs on the chloride conductance induced by exogenous GABA in single neurones. Figure 2 schemati-

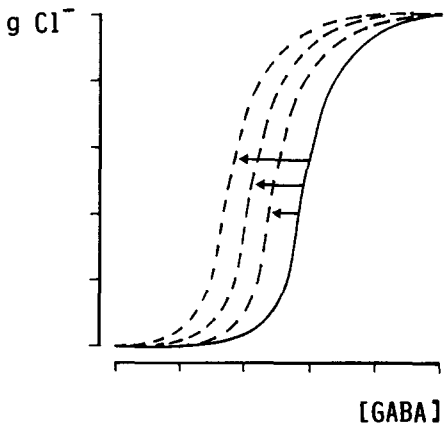

Fig. 2. Dose-dependent parallel leftward shift of the GABA dose-response curve by a benzodiazepine receptor agonist. *Ordinate:* chloride conductance (g Cl^-). *Abscissa:* log dose of GABA

cally summarizes the results of such studies: the dose-dependent, parallel shift of the GABA dose-response curve to the left without change in the maximum GABA effect. This increase of the apparent potency of GABA in the presence of BZs indicates that the facilitation of GABAergic transmission at any synapse will depend on the dose of the BZ and the concentration of GABA in the synapse: BZs cannot increase maximally active GABAergic transmission but increase submaximally synaptic efficiency. The effect of BZs is highly specific, as other inhibitory transmitters and excitatory transmitters are not affected even up to high concentrations.

Studies like those just mentioned on isolated neurones in cell culture suggested that BZs did not act on presynaptic mechanisms of GABAergic synapse, but rather at the level of $GABA_A$ receptors (signal recognition) or at post-receptor events (signal transduction). The identification of specific receptors for BZs (BZR) made it possible to localize the site of action.

Using highly radioactive BZs, initially ^{3}H-diazepam, it was shown that these drugs bind with high affinity (in the low nanomolar range) and high specificity to saturable sites (glycoproteins) in neuronal cell membranes from the CNS (Squires and Braestrup 1977; Möhler and Okada 1977). The distribution of these BZRs is visualized in autoradiograms of brain slices incubated with a radioligand (Fig. 3) or after intravenous injection into an animal (Richards et al. 1986). Using ligands labeled with a positron-emitting, short-lived radionuclide (e.g. ^{11}C), the receptors can be visualized in the intact animal and human brain by PET scanning procedures (Samson et al. 1985). Early studies indicated that BZs did not block the binding of GABA to the $GABA_A$ receptor but, surprisingly, increased this binding (Costa et al. 1978). Moreover, the binding of BZs to their receptors was found to be increased in the presence of GABA (Tallman et al. 1978). This suggested a close functional interaction between the BZR and the $GABA_A$ receptor. That this coupling is not only functional, but also physical, was shown when the BZR was solubilized from neuronal cell membranes with detergents and isolated. The purified glycoprotein material precipitated by monoclonal antibodies bound BZs as well as GABA (Schoch et al. 1985), pointing to the existence of a macromolecular complex (approximately 220 kD molecular mass) with both GABA and BZ binding sites. This complex was shown to be composed of two subunits (α- and β-subunit) of about 55 kD molecular masses. Antibodies raised against the two subunits made it possible to visualize the BZRs by immunohistochemistry and to demonstrate the same distribution as revealed by autoradiography with labeled BZs and the selective $GABA_A$ agonist muscimol (Häring et al. 1985). The recent elucidation of the primary structure of the receptor complex has confirmed the suggested molecular organization of the $GABA_A$-BZR-chloride channel.

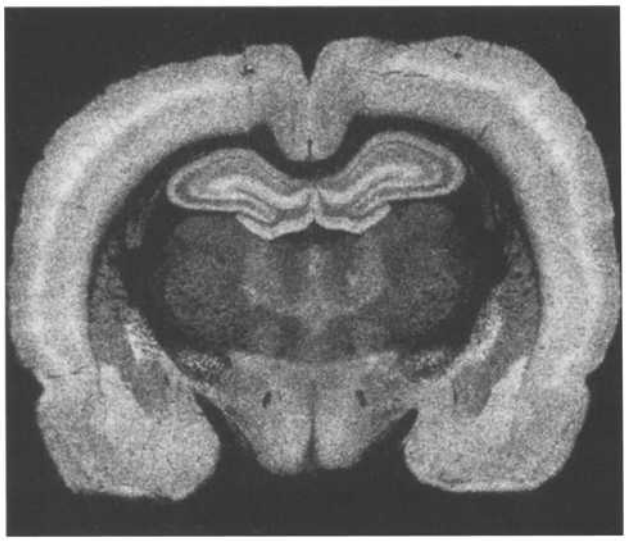

Fig. 3. Autoradiographic visualization of benzodiazepine receptors in the rat brain using ^{3}H-flumazenil (courtesy of Dr. J. G. Richards)

The $GABA_A$-BZR-Chloride Channel Complex

Using molecular genetic techniques, complementary desoxyribonucleic acids (cDNA) to the messenger ribonucleic acids (mRNA) of the bovine brain coding for the α- and β-subunit of the receptor-channel complex were cloned and sequenced (Schofield et al. 1987). The primary structures of the protein subunits were deduced from the cDNAs. They show four hydrophobic sequences of about 20 amino acids long, which are likely to form α-helices and to anchor as transmembrane segments the subunits in the lipid bilayer, as well as a large extracellular N-terminal segment containing potential glycosylation sites. This extracellular part would contain the BZ binding area (in the α-subunit) and the GABA binding area (in the β-subunit); the number of binding areas per subunit is not yet known. A small cytosolic domain of the β-subunit contains a potential phosphorylation site. The similarity of the structure of these subunits to those of the nicotinic cholinoceptor (containing a cation channel) and of the glycine receptor (containing a chloride channel) suggests the existence of a family of receptor-coupled ion channels with similar principal secondary and tertiary structure (Fig. 4). The injection of natural mRNAs or cDNA-derived RNAs for the α- and β-subunits into frog oocytes, which do

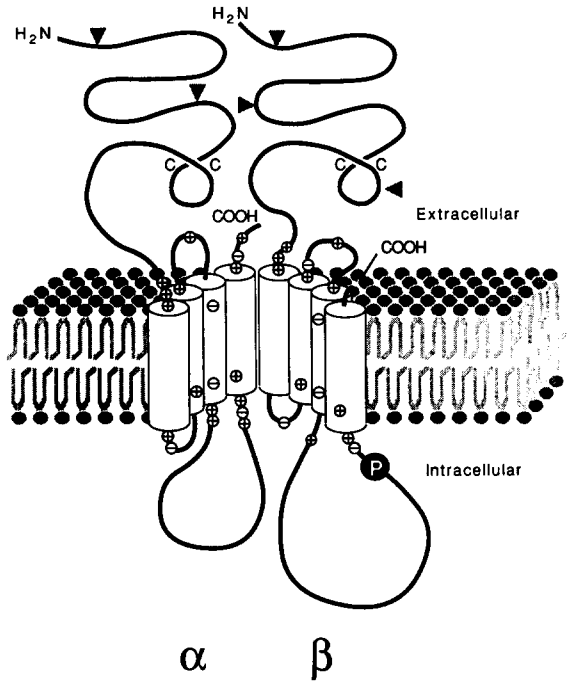

Fig. 4. Suggested domain (extracellular, transmembrane, cytoplasmic) arrangement of the α- and β-subunits of the $GABA_A$-BZR-chloride channel (Reproduced with permission from Schofield et al. 1987)

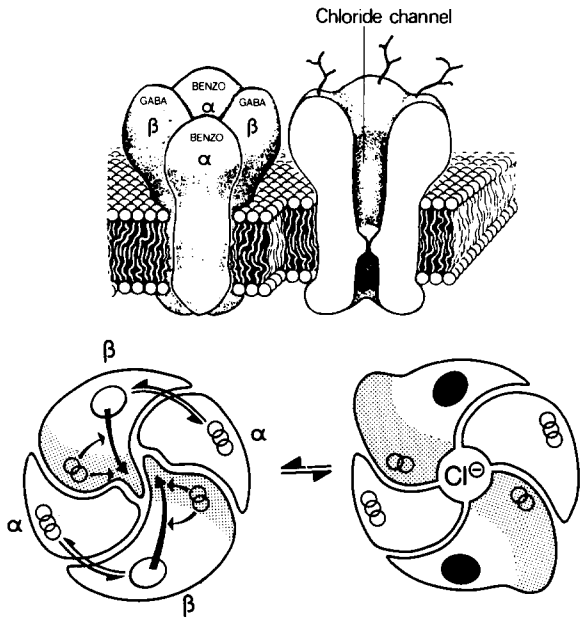

Fig. 5. Hypothetical model of the $GABA_A$-BZR-chloride channel

not normally contain $GABA_A$ receptors, led to the synthesis and membrane incorporation of fully functional $GABA_A$-BZR-chloride channel (Schofield et al. 1987). The complex appears to be a tetraheteromer with a subunit stoichiometry of $a_2\beta_2$ (Fig. 5).

The BZR as an Allosteric Modulatory Site of the $GABA_A$ Receptor

BZs in the absence of GABA have no effect on the chloride conductance of neurones, i.e. they do not operate the chloride channel. However, when present at the BZR, they modify the gating function of the $GABA_A$ receptor. The BZR is, therefore, an allosteric modulatory site of the $GABA_A$ receptor. The concept of allosteric modulation is well known in enzymology and involves the notion that a ligand binding to a specific site of an enzyme different and distant from the active (catalytic) site itself may alter the function of the latter. By analogy, the BZR is an allosteric modulatory site of the $GABA_A$-receptor-chloride channel and the mutual allosteric modulation of GABA and BZ binding reflects the interaction between two receptor domains on the same oligomeric protein. The allosteric interaction requires that the ligand bound to the BZR induces a conformational change in this domain that is transmitted intramolecularly to the $GABA_A$ receptor, which might in turn undergo a conformational change resulting in an increased affinity for GABA. In addition, the BZR ligand-induced conformational change may facilitate the channel gating mechanism, i.e. the GABA-induced transition of the complex from the closed into the open channel conformation.

The Various Ligands of the BZR

The function of the BZR reveals complexities hitherto not encountered within other receptors (Haefely 1987).

The discovery of the first BZ antagonist, flumazenil, in 1979 in our laboratories (Hunkeler et al. 1981; Haefely and Hunkeler 1988) was not our goal at that time but, nevertheless, was not entirely unexpected for theoretical reasons. Indeed, the interaction of ligands (natural signal substances or exogenous compounds) with their receptors is governed by two intrinsic properties of the ligands, namely by their *affinity* to bind to the receptor (signal recognition by the receptor) as well as by their capability to induce a functional change in the receptor (underlying signal transduction function of the receptor), called *intrinsic efficacy*. Ligands capable of activating a receptor are called *agonists* and are said to possess intrinsic efficacy; ligands unable to activate the receptor but blocking the access of agonists to the binding site are called *antagonists* and have (ideally) zero intrinsic efficacy. The antagonist flumazenil binds with high affinity to BZRs but produces negligible BZ-like effects. However, it prevents, when given before, and reverses,

when given afterwards, the effects of diazepam and other BZ tranquilizers. We therefore proposed to call agents of the latter category agonists, and flumazenil and similarly acting agents, antagonists at the BZR. Flumazenil is now available for therapeutic use and is administered intravenously to reverse coma after suicidal or iatrogenic overdosage with BZR agonists and to accelerate the recovery from anaesthetic procedures involving BZs. The effect of flumazenil is highly specific for agents acting at the BZR and does not antagonize other central depressants, e.g. barbiturates or ethanol.

The existence of agonists and antagonists of the BZR is in line with the general knowledge on ligand-receptor interactions. Moreover, ligands have also been found that have an intrinsic efficacy between that of the classic agonists and that of antagonists. They are called *partial agonists* and are of remarkable potential interest as drugs, because they still have anxiolytic and anticonvulsant properties but are less efficacious in producing the sedative and muscle relaxant effects of full agonists, thus behaving as mixed agonists-antagonists. Further interesting properties are greatly reduced tolerance, ethanol potentiation and physical dependence liability. Ro 16-6028 (Martin et al. 1988) is one of these partial agonists in clinical trials.

Quite unexpectedly, other compounds were found almost simultaneously with flumazenil: BZR antagonists which bind specifically to the BZR, however, have pharmacological properties that are in every respect opposite to those of BZR agonists; they are anxiogenic, convulsive, vigilance enhancing and spasmogenic. Their effects are promptly reversed by flumazenil and other BZ antagonists, demonstrating without any doubt that their effects are mediated by the BZR. As one would expect, they reduce the effect of GABA on chloride conductance. In contrast to agonists the binding of which is increased by GABA, and to antagonists whose binding is unaffected by GABA, the binding of these agents is decreased by GABA. To account for all these properties we have proposed naming these agents *inverse BZR agonists*, because they produce an effect through the BZR (and, hence, are agonists) and because this effect is the opposite of that of agonists (Polc et al. 1982). Inverse agonists can be ascribed a negative intrinsic efficacy or negative modulatory action on the $GABA_A$ receptor. They are found in various chemical classes, e.g. β-carboline derivatives, benzodiazepines. Figure 6 is a schematic presentation of the BZR ligands with intrinsic efficacies ranging from +1 (full agonists) over zero (pure antagonists) to −1 (full inverse agonists). As indicated in this oversimplified model, all ligands attach to the same binding area or to overlapping binding areas of the BZR.

Receptors other than the BZR that mediate two opposite effects have not yet been found. Possible explanations for this peculiar property of BZR have

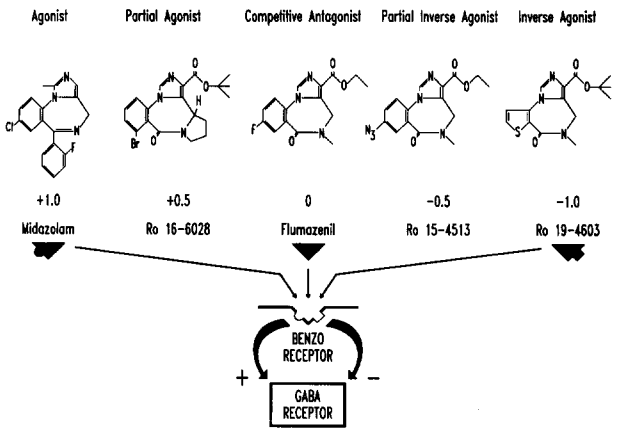

Fig. 6. Prototypes of benzodiazepines with differing intrinsic efficacies

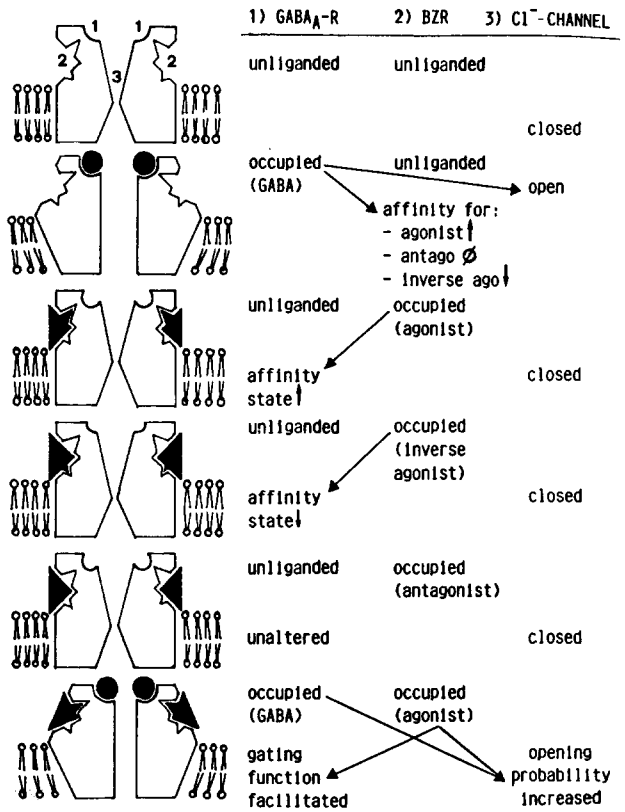

Fig. 7. Schematic presentation of the different states of the $GABA_A$-BZR-channel complex induced by various ligands of the GABA (1) and BZ (2) binding sites. It is assumed that the three prototype ligands of the BZR interact with common or distinct but overlapping regions of the binding area

been proposed (see Haefely 1988b, c), the major one being that the BZR is not involved in primary signal transmission, but in allosteric modulation of the latter, thus being a kind of secondary receptor modulating the primary one. Considering only the GABA binding site and the BZ binding site, a multiplicity of different states of the $GABA_A$-BZR-chloride channel can be thought to occur, the major ones being shown in Fig. 7.

Modulation of the $GABA_A$ Receptor Function by the BZR and Pharmacological and Therapeutic Effects of BZR Ligands

$GABA_A$ receptors and, therefore BZRs are ubiquitous in the CNS. One would, therefore, expect BZR ligands to affect a large number of central nervous functions. This is indeed the case. There can be little doubt that disorders such as anxiety and related disorders, as well as convulsive states, have as their biological basis a pathologically high activity of critical neurones and neuronal networks, and it is plausible that the beneficial effects of BZR agonists and the anxiogenic and convulsive effects of BZR inverse agonists are due to an improvement or impairment, respectively, of GABAergic efficiency. The evidence is also straightforward that GABAergic neurones normally function to dampen vigilance, muscle tone and a series of centrally controlled vegetative and hormonal functions, which explains the sedative, muscle relaxant and autonomic stabilizing actions of BZR agonists. Precisely which CNS regions and which neuronal networks are involved in these various states of the CNS remains to be determined. The various ligands of the BZR will prove to be very useful tools in this endeavour.

Open Questions

Knowledge of the exact three-dimensional structure of the $GABA_A$-BZR-chloride channel complex, requiring X-ray studies of crystalline pure material (to be obtained by the recombinant DNA technique), will allow us to understand the *molecular organization of the complex,* to map the *structure of the GABA and the BZ binding site* and to reveal the *open and closed conformations of the channel.* It will be extremely important to see in detail how the various classes of BZR ligands interact with the binding site (i.e. which parts of the ligand molecule form reversible bonds with which atoms and atomic groups of the receptor binding area) in order to understand why small changes in the ligand structure affect affinity and intrinsic efficacy (Haefely et al. 1985).

Many receptors are known to occur in slightly differing structures or forms (heterogeneity), owing to the existence of different genes, differing post-transcriptional or post-translational processing (e.g. degree of glycosylation). Some observations compatible with *structural microheterogeneity of BZRs* have been made; however, the irrefutable proof for this heterogeneity is still lacking. The role of the carbohydrate moiety of the receptor is also unknown.

A very exciting issue is the question whether the BZR is affected by *endogenous ligands* in normal or pathological conditions. It is, indeed, very tempting to assume that anxiety and epilepsy might be due to the occurrence of an endogenous ligand with inverse agonistic property or the lack of an endogenous compound with agonistic activity. Various reports have claimed the discovery of endogenous BZR ligands in brain extracts, detected by their ability to inhibit the binding of radioligands to the BZR. None of these putative endogenous ligands has proven to act in the proposed way (Haefely 1988a). A widely held view argues that a receptor would not exist without a functional need and without a corresponding endogenous ligand. However, it should also be taken into consideration that a macromolecule inevitably contains on its large surface patches to which a variety of small exogenous molecules happen to fit. This is, of course, not the case for a receptor operating a channel or an enzyme, but may not be illogical in the case of non-essential allosteric modulatory sites.

The search for an endogenous ligand of the BZR has recently resulted in the unexpected identification of BZs in the brain and other tissues in humans and animals, most of them being BZs used in therapy, e.g. diazepam and nordiazepam (Wildmann et al. 1987). The concentrations are extremely low and their presence has been demonstrated in plants largely used as nutrients, e.g. potatoes and cereals. It appears that some plants and/or microorganisms are able to synthesize BZs with activity at the BZR. These compounds are probably not endogenous ligands of the animal and human organism but are *natural BZs.* It is ironic that BZ tranquilizers, considered by many to be classic representatives of the "unnatural" and evil products of the pharmaceutical industry, were produced by nature long before it occurred to a chemist to synthesize a seemingly novel molecule (Haefely 1983).

Research on the mechanism of action of BZs has not only resulted in the identification of the target molecule for these drugs but has been instrumental in revealing an unexpected complexity of one of the most vital neurotransmitter receptors, the $GABA_A$

receptor. The impact of BZR ligands on the exploration of physiological and pathological functions of the CNS is likely to be important.

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