벤조다이아제핀 수용체 이상과 불안장애

(GABA$_A$-Benzodiazepine Receptor)

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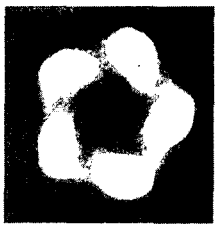
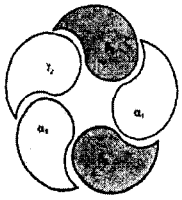
History of GABA$_A$-Benzodiazepine Receptor

- Mid-1950s ; clinical use of the first benzodiazepine
- 1974 ; highly specific potentiation of GABA by BZ (Roche)
- 1977 ; BZ interacted with specific binding site in the CNS, *which turned out to be an integral part of the* GABA$_A$ receptor complex
- 1987 ; receptor complex was isolated and sequenced
- 1994 ; visualized by electron microscopy

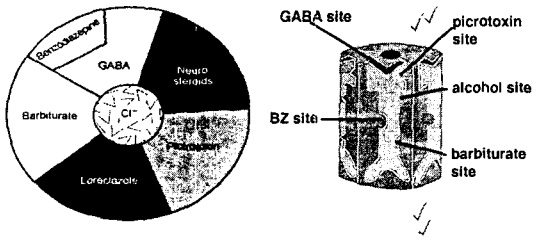
GABA$_A$-Benzodiazepine receptor complex





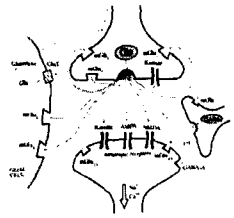
by EM (Nayeem et al 1994)

Schematic representation of the binding sites on the GABAA-benzodiazepine receptor complex



GABA and Anxiety

- An imbalance of the GABA and glutamate systems, in addition to other NT systems, has been hypothesized to underlie pathological anxiety
- *Attenuation of the GABAnergic* system : arousal, anxiety, restlessness, and insomnia
- Favor of GABA : sedation, amnesia, ataxia

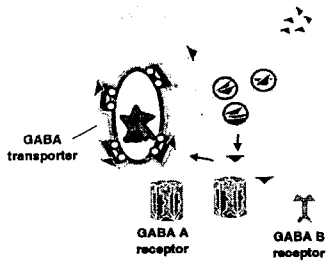


Kent et al. Biol Psychiatry 2002;52:1008-1030

Early Classification of GABA receptors

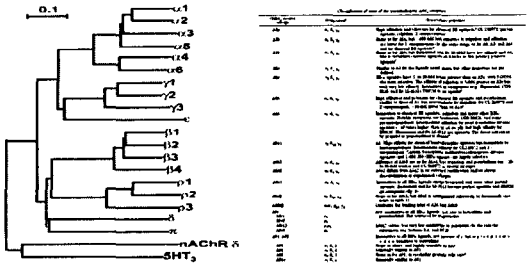
- $GABA_A$ receptors ; gatekeeper for a chloride channel, allosterically modulated by a potpourri of nearby channel
- $GABA_B$ receptors ; selectively binding to the baclofen not allosterically modulated by benzodiazepines
- Benzodiazepine receptors
- $GABA_C$ receptor ; insensitive to both bicuculline and baclofen
- Excitatory $GABA_A$ receptors ; GABA can be an excitatory transmitter at certain loci in embryonic and early postnatal life
  ; tonically stimulated adult hippocampal pyramidal neurons

GABA RECEPTORS



Structures of the $GABA_A$ receptors

- Cloning form cDNA libraries or genomically → *19 related* $GABA_A$ *receptors*



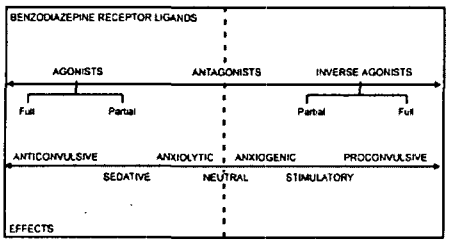
BZ receptors

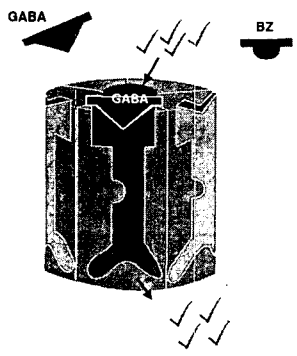
- Five BZ receptor subtypes – 3 distinct pharmacological profiles
  - BZ 1(omega 1) receptor
    : preferentially located in the cerebellum and contain recognition sites with high affinity both for BZ and for agents with different chemical structures
    : mediating anxiolgytic action and sedative-hypnotic action
  - BZ 2(omega 2) receptor
    : located predominantly in the spinal cord and striatum
    : mediating the muscle relaxant action BZ
  - BZ 3(omega 3) receptor
    : peripheral type, abundant in the kidney
    : unclear in anxiolytic actions

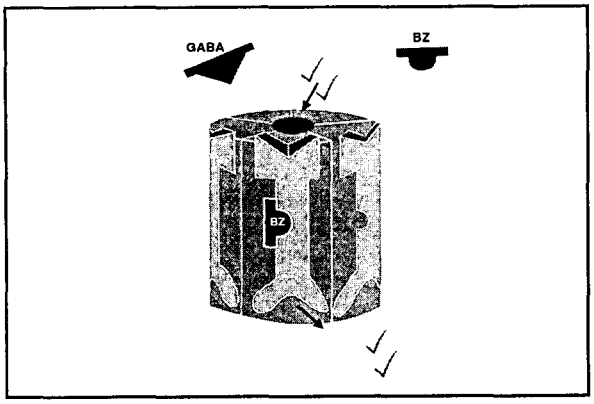
$GABA_A$-BZ Receptor Complex

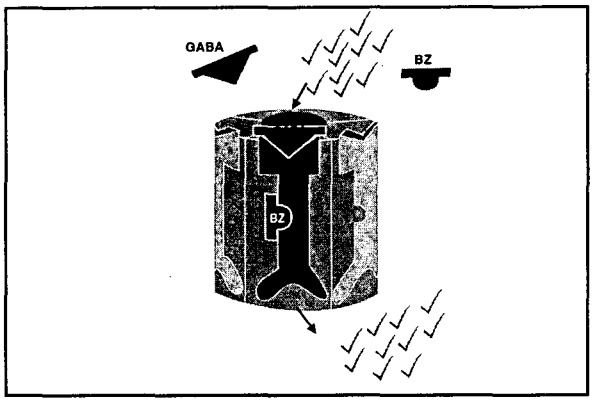
- BZ-BZ receptor binding → allosetrically changes the receptor complex to increase the efficiency of GABA
  --> enhance the effectiveness of the GABA (lowering the concentration of GABA required for opening the channel)
  → safer(brain circuits cannot be inhibited over and above the level that would be achieved by natural GABAergic effects
- Barbiturate, chloral hydrate, ethanol -> directly open the chloride channel(fatal in overdose)

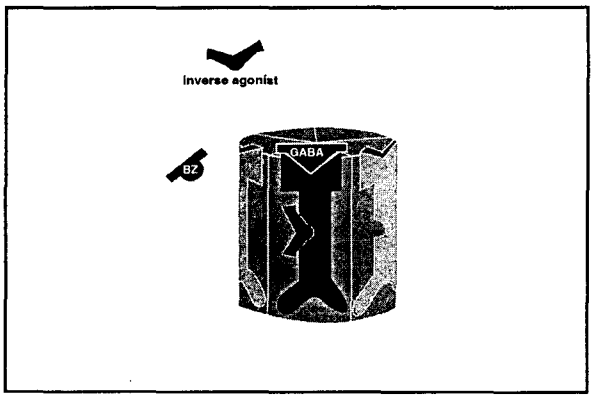
Agonists, antagonists, inverse agonist

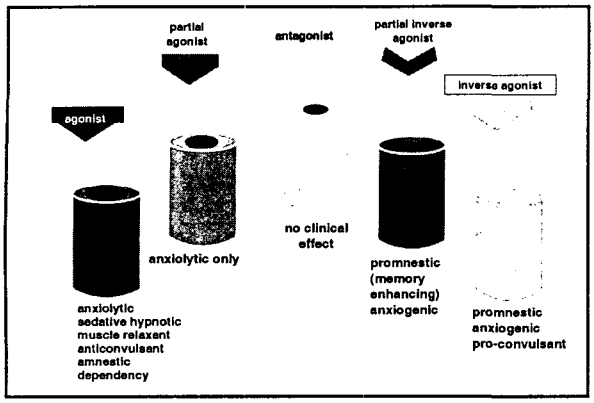


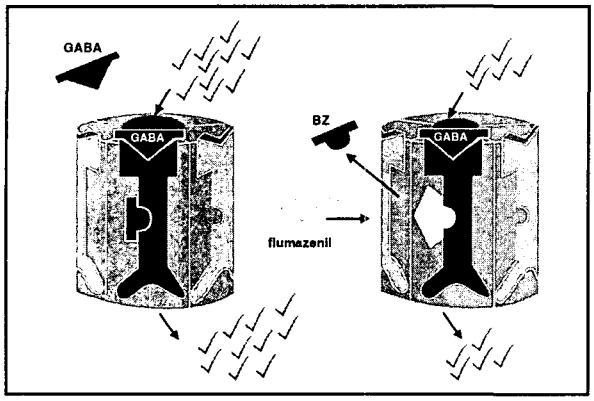


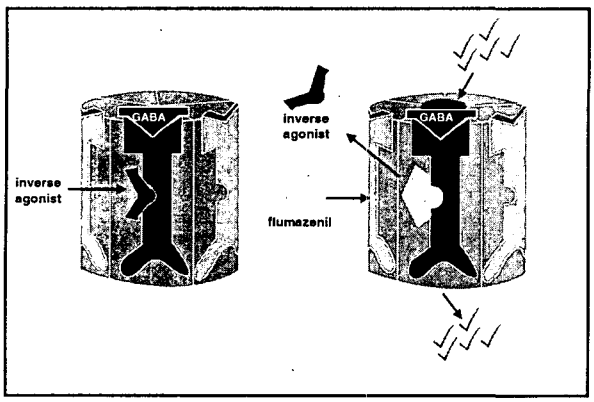

GABA
BZ
BZ


GABA
BZ
BZ


Inverse agonist
BZ
GABA


partial agonist
antagonist
partial inverse agonist
inverse agonist
agonist
anxiolytic only
no clinical effect
promnestic (memory enhancing) anxiogenic
promnestic anxiogenic pro-convulsant
anxiolytic sedative hypnotic muscle relaxant anticonvulsant amnestic dependency


GABA
GABA
BZ
GABA
flumazenil

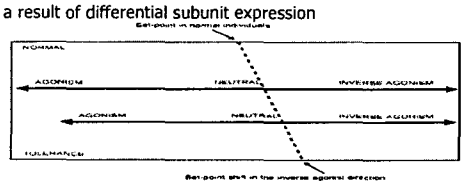

GABA
inverse agonist
GABA
inverse agonist
flumazenil

BZ receptor site : evolutional pressures ?

- **Necessary to regulate anxiety : brain itself produces an anxiety-reducing compound(endogenous agonist)**
  - anxiety and insomnia = deficiency of this compound production
    -> continual long-term replacement Tx ?
  a. found in brains of individuals who died long before the first labo. synthesis of BZs (Sangameswaran et al 1986)
  b. endogenous BZ agonists(endozapnes) are found in the rare familial condition, idiopathic recurrent stupor(Tinuper et al 1994), hepatic encephalopathy(Cossar et al 1997)
  c. Aspergillus fungi can make a range of BZs and these naturally occurring BZs can also be stored in human brains after being eaten

- **To mediate the activities of endogenous inverse agonists**
  -> keep brain arousal optimal and if levels fell, sleep could result
  a. ethyl-betacaboline-3-carboxylase(beta-CCE) : first compound to promote anxiety by direct action at a receptors in the brain(Braestrup et al 1980)
  - not endogenous, being formed in the extraction process
  b. Tribulin : elevated levels in increased anxiety(PTSD, alcohol withdrawal)(Glover 1998)
  - structure has not been determined

- **No endogenous BZ receptor ligand and that the site may simply be a particular protein conformation that "fine tunes" GABA functions**
  → altering maximal efficacy, or the rate of desnsitisation
  a. BZ receptor spectrum is not fixed and that the "set-point " – where drug bind, but have no effect- can be moved, perhaps as a result of differential subunit expression



Anxiety : BZ receptor abnormality ?

- **BZ receptor antagonist " flumazenil" as a challenge test and as an imaging ligand**
  a. 2 mg of flumazenil(occupy more than half of the receptors in the brain) → provoked panic in most of the patients but was quite innocuous in the control subjects(Nutt et al 1990, Woods 1991, Maddock 1998, Strohle et al 1999)
  → displacement of an endogenous agonist(only in patients)
  → set-point of the BZ receptors has moved in the inverse agonist direction, making flumazenil a weak inverse agonist

Neuroreceptor Mapping -GABA

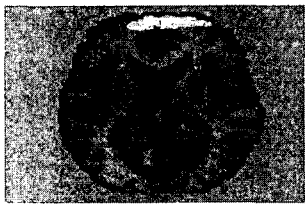
- **PET neuroreceptor ligands : [^{11}C] flumazenil**
- **SPECT neuroreceptor ligands : [^{123}]iomazanil**
  [^{123}]NNC 13-8241

< PET SCAN >
Left : normal brain
Right : Panic disorder

GABA-BZ receptor and Anxiety

- Panic disorder : reduced GABAA-BZ receptor binding capacity in several brain region
  - frontal lobe(Schlegel et al 1994, Kaschka et al 1995, Kuikka et al 1995)
  - temporal lobe(Schlegel et al 1994, Kaschka et al 1995)
  - hippocampus(Brenner et al 2000)
  - occipital cortex(Goddard et al 2001)
- GAD : reduced binding in the temporal lobe(Tihonnen et al 1997)
- PTSD : reduced binding in the prefrontal cortex(Brenner et al 2000)

Decreased BZ receptor binding in PTSD



Results

Dis

Magnetic Resonance Spectroscopy

Study	Diagnosis	Region	Finding
Sanacora et al, 1999	Depression	occipital	52% reduction in GABA
Behar et al, 1999	ETOH depen.	occipital	25% reduction
Hetherington et al, 2000	cocaine abuse	occipital	23% reduction
Goddard et el, 2001	panic disorder	occipital	22% reduction
Ke et al, 2001	cocaine abuse	prefrontal	10-20% reduction
Epperson et al, 2002	PMDD	occipital	reduced GABA during the follicular phase

Conclusion

- **BZs work at specific receptor sites on the $GABA_A$ receptor complex in the brain, and subtypes of these receptors mediate different actions**
- **Abnormality of BZ receptors may underlie some anxiety disorders**
  - **reduction in GABAA-BZ receptor binding in the cortex in panic disorder, GAD, PTSD**
  - **defective neuroinhibitory processes play a role in the pathophysiology of anxiety disorders**
- **Drugs targeted at specific receptor subtypes may offer the hope of anxiolytics without unwanted side-effects**