ANTI ELEPTIC PROPERTY OF BRETAZENIL

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ABSTRACT

Bretazenil, a benzodiazepine receptor partial agonist, has demonstrated potential therapeutic applications in various neurological disorders. Although not explicitly studied for its antiepileptic properties in clinical trials, its mechanism of action, which involves enhancing GABAergic inhibition, suggests it could have beneficial effects in epilepsy. Given the role of GABA in regulating neuronal excitability, bretazenil's ability to modulate this neurotransmitter system may offer a potential avenue for epilepsy treatment. However, further research, including controlled clinical trials, is necessary to validate its efficacy and safety in patients with epilepsy.

KEYWORDS: Epilepsy, Seizures, Bretazenil, GABA-A Receptor, Benzodiazepine.

INTRODUCTION

Bretazenil was first developed as an anti-anxiety drug, though studies have also looked into its possible anticonvulsant properties. but has never been produced for a profit. It acts as a partial agonist for the benzodiazepine site of the brain's GABA-A receptors. Bretazenil, according to David Nutt of the University of Bristol, shows many of the positive traits of alcohol intoxication, such as sociability and relaxation, without the negative traits of aggression, amnesia, nausea, loss of coordination, liver disease, and brain damage. This makes it a promising candidate for development into a more potent social drug. In contrast to alcohol, which cannot instantly reverse the effects of bretazenil, flumazenil is an antidote for benzodiazepine overdose {Thijs RD *et al.,*2019}.

The benzodiazepine class of drugs includes the anxiolytic medication bretazenil, which was created in 1988. Although its actions differ slightly, it shares structural similarities with the benzodiazepine antagonist flumazenil

Based on a large double-blind placebo-controlled experiment, bretazenil appears to be a highly effective anxiolytic drug in GAD, exhibiting similar action to diazepam. Both bretazenil and diazepam have been linked to some rebound effects {Sen A *et al.,*2020}.

The frequency of side effects (such as drowsiness) in this trial was less common than with diazepam and was comparable to the placebo. However, sedative side effects were noted in the two investigations on bretazenil in panic attacks mentioned below. The potential sedative effects of bretazenil in healthy volunteers are not well documented. However, in a comparative study designed to assess abuse potential, bretazenil was found to cause decreases in

psychomotor performance and subjective impressions of sedation. These effects were less pronounced than those of the two full agonists tested, and the dose-response curve was shallow. The pharmacokinetic profile of bretazenil was found to be inadequate, leading to the suspension of the compound's clinical development. Bretazenil's duration of action is rather brief in humans, making it unsuitable for daily anxiety treatment {Gameli PS *et al.,*2024}.

Over 70 million individuals worldwide suffer from epilepsy, one of the most prevalent brain affordable treatments for epilepsy that can significantly lower morbidity, disability, and death, it should be a top priority for global health. The WHO, the International League Against Epilepsy, and the International Bureau for Epilepsy started the Global Campaign Against Epilepsy in 1997. As a result, all governments were urged to address the unique needs of individuals with epilepsy in the 2015 World Health Assembly.

Figure 1.1

Type Of Epilepsy

1. Idiopathic generalized epilepsies

The relatively common idiopathic generalized epilepsies include those characterized by generalized tonic-clonic seizures (23%), absence epilepsies (6%), and myoclonic epilepsies (3%){Rana A *et al.*,2018}. There is strong evidence that compared to simple or complicated

partial seizures, generalized tonic-clonic seizures are more likely to impair cognitive skills. The risk of cognitive impairments beyond that of epilepsies with generalized tonic-clonic seizures is only increased by the presence of status epilepticus. Whether the thalamus or the cortex is where initial generalized epilepsies seizures start is still up for debate. Furthermore, a large body of research suggests that in generalized epilepsies, frontal lobe structures are primarily responsible for eliciting epileptic activity. Neuropsychological tests reveal impairment of prefrontal processes such as mental flexibility and working memory, which correlates with electrophysiological evidence. These findings are linked to lower prefrontal glucose metabolism and N-acetyl aspartate (NAA) concentrations found in functional brain imaging studies. Additionally, patients with primary generalized epilepsy had anomalies in their frontal lobes as evidenced by MRI morphometry. In summary, patients with primary generalized epilepsy exhibit abnormalities in the frontal lobe structures as shown by EEG, cognitive testing, and functional and structural brain imaging analyses. These frontal deficiencies do not, however, indicate global epilepsies. Frontal functions may be impaired similarly or even more severely in focal epilepsies of temporal, parietal, and frontal origin {Witkin JM *et al.,*2024}.

2. **Symptomatic focal epilepsies**

Temporal lobe epilepsies, frontal lobe epilepsies, parietal lobe epilepsies, and occipital lobe disorders. It has multiple neurological, cognitive, and psychosocial repercussions and is typified by a persistent propensity to produce spontaneous epileptic seizures. People with epilepsy make up about 80% of the population in low- and middle-income nations. People with epilepsy may not receive treatment since the condition is stigmatized in many parts of the world. More than 75% of people with active epilepsy go untreated, creating a significant treatment gap that is primarily found in low- and middle-income nations. Since there are epilepsies are the four primary localization-related epilepsies suggested by the International Classification of Epilepsies. Except for hippocampal sclerosis, none of these localization-related epilepsies have known causes or etiologies. Most people agree that the high prevalence of discrete syndrome known as temporal lobe epilepsies associated with hippocampal sclerosis exists. As a result, the neuropsychological features of mesial temporal lobe epilepsies are covered in isolation{ Perucca P *et al .,*2018}.

3. **Mesial temporal lobe epilepsy**

Temporal lobe epilepsy is the focal epilepsy that occurs most often. Histological examinations showed that most individuals with temporal lobe epilepsy (70%) exhibit hippocampal sclerosis. Antiepileptic drugs often do not provide adequate control for mesial temporal lobe epilepsy

(MTLE). Hence, individuals with MTLE are probable candidates for surgery to treat epilepsy. Neuropsychological evaluation is an important part of the presurgical assessment for patients with MTLE, leading to thorough research on the neuropsychology of this condition. Most patients with MTLE experience prominent signs of episodic memory problems, which can be either related to specific materials or not, caused by structural lesions in the hippocampal formation. Word-finding deficits are frequently noticeable in patients with MTLE of the hemisphere dominant for speech {Perucca E *et al*.,2023}. Word-finding deficits are believed to be caused by the regular spread of epileptic activity into temporolateral regions. Furthermore, MTLE is commonly linked with moderate deficits in cognitive abilities, academic performance, language skills, and visuospatial skills. Prefrontal lobe functions, such as attention and executive functions, are often preserved. Patients with secondarily generalized tonic–clonic seizures have a high risk of experiencing both general cognitive impairment and specific deficits in prefrontal lobe functions. Patients with MTLE who experience generalized tonic–clonic seizures may exhibit metabolic disruptions in the prefrontal region. It is probable that these metabolic imbalances are linked to cognitive impairment and reductions in executive functions.

4. Frontal lobe epilepsy

Epilepsy with involvement of the frontal lobe is the second most common type of localization-related epilepsy. The early symptoms of frontal lobe seizures vary depending on where the epileptogenic zone is located. Focal clonic motor seizures occur due to epileptic activity in the primary motor cortex. Tonic seizures start in the supplementary motor area (SMA), while complex partial seizures start in various frontal regions such as orbital frontal, mesial frontal, frontal polar, and dorsal lateral regions. The range of symptoms of frontal lobe seizures and associated neuropsychological deficits reflects the intricate and varied functions of the frontal lobe. Neuropsychological research compared the cognitive impacts between individuals with frontal lobe and temporal lobe epilepsy and those without the condition{Penovich PE *et al*.,2024}. Patients with epilepsy in the frontal lobe exhibited decreased attention span and psychomotor speed, while those with epilepsy in the temporal lobe experienced difficulties with episodic memory. The differences between the two patient groups are likely influenced by the location and age-related aspects of frontal lobe lesions. As previously noted, dysfunction of prefrontal structures is common in MTLE patients with secondarily generalized tonic-clonic seizures. Additionally, the age when frontal lobe epilepsy first appears could greatly impact the likelihood of certain frontal impairments. Epilepsy affecting the parietal and occipital lobes.

Occipital and parietal lobe epilepsy have low occurrence rates for both prevalence and incidence. Thus, there has been no published extensive and organized neuropsychological examination of adult individuals with occipital or parietal epilepsy. Various types of benign childhood epilepsies and epilepsies with bilateral occipital calcification and encephalomyopathy with lactic acidosis and stroke like episodes (MELAS) are among the acknowledged syndromes affecting the parietal and occipital regions. In adults, epilepsies affecting the parietal and occipital lobes are commonly caused by traumatic injuries, cortical development malformations, and tumors .Sexual sensations, apraxias, and disturbances in body image have been recorded as auras or ictal phenomena in individuals with parietal lobe epilepsy, along with paresthetic, dysesthetic, and painful symptoms. It is common for parietal ictal activity to diffuse into the frontal lobe, which can significantly alter postictal and ictal symptoms. The precise function of the parietal lobe in linguistic and spatial cognition has long been a matter of debate. Language impairments, hemineglect, apraxia, visuospatial and constructive problems, and visual associative agnosia can all result from parietal lobe lesions. Performance on nearly all nonverbal tasks of IQ tests is significantly hampered by mass lesions of the nondominant parietal lobe{Niquet J *et al*.,2019}. Severe receptive aphasia can be brought on by lesions in the speech-dominant hemisphere's temporoparietal junction. Depending on the lateralization and localization, patients with parietal lobe epilepsy may experience a wide range of cognitive symptoms.

5. Parietal and occipital lobe epilepsy

Occipital and parietal lobe epilepsy are rather uncommon in terms of prevalence and incidence. There hasn't been a published thorough and organized neuropsychological analysis of adult individuals with parietal or occipital epilepsy. Parietal and occipital epilepsy syndromes that are recognized include encephalomyopathy with lactic acidosis and strokelike episodes (MELAS), many forms of benign childhood epilepsies, and epilepsies with bilateral occipital calcification. Adult parietal and occipital lobe epilepsies are frequently caused by trauma-related lesions, tumors, and abnormalities of cortical development. Sexual sensations, apraxias, and disturbances in body image have been recorded as auras or ictal phenomena in individuals with parietal lobe epilepsy, along with paresthetic, dysesthetic, and painful symptoms. It is common for parietal ictal activity to diffuse into the frontal lobe, which can significantly alter postictal and ictal symptoms{Neri S *et al*.,2022}.

The precise function of the parietal lobe in linguistic and spatial cognition has long been a matter of debate. Language impairments, hemineglect, apraxia, visuospatial and constructive

problems, and visual associative agnosia can all result from parietal lobe lesions. Large lesions in the nondominant parietal lobe significantly reduce performance on nearly all nonverbal IQ test tasks. Severe receptive aphasia may result from lesions around the speech-dominant hemisphere's temporoparietal junction. Depending on the lateralization and localization, age of injury, and age of epilepsy onset, patients with parietal lobe epilepsy may experience a wide range of cognitive symptoms{Brigo F *et al*., 2019}.

Basic hallucinations often manifest as auras in patients with occipital lobe epilepsy. Nystagmoid eye movements, blinking, ictal blindness, and eye deviation are other ictal symptoms. Frontal and temporal regions frequently experience an ictal spread. Idiopathic occipital lobe epilepsy patients' cognitive function profile does not appear to be significantly different from that of other epilepsy patients.

❖ Etiology

Just about every cerebral disease that makes brain tissue more excitable might cause seizures. Genetic and acquired brain lesions are the two categories into which the etiologies can be subdivided. Additionally, it might be widespread, multifocal, or focal. This article does not include juvenile or infantile epilepsy disorders that have a predominately genetic origin (such as Lennox-Gastaut syndrome). Adult traumatic brain injuries, malignancies, central nervous system infections, and neurodegenerative disorders are the most common etiologies. In certain individuals, it is impossible to rule out numerous etiologies. A few etiologies become more common as people age. Brain tumors, arteriovenous malformations, and head injuries are the most common etiologies in people aged 20 to 40. In young adults, residual epilepsy resulting from early CNS injury (such as cerebral palsy) is relevant. Brain tumors, both primary and metastatic, and neurological diseases such as Alzheimer's dementia are most common in people over 60 {Balestrini S *et al*., 2021}.

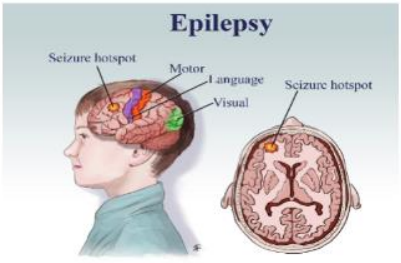


Figure 2

1. Cerebrovascular disease

Acquired epilepsy in the Western population is primarily caused by cerebral vascular dysfunction. In an extensive community-based investigation, cerebrovascular disease was found in 15% of patients with newly diagnosed epilepsy. Even fifty percent of epilepsies that occur after the age of sixty are caused by cerebrovascular problems. The risk of epilepsy following hemorrhagic strokes is significantly higher than following ischemic strokes. Subarachnoid hemorrhage carries a 20% one-year risk of epilepsy, which rises if a middle cerebral artery aneurysm has been surgically removed. For patients with arteriovenous malformations (AVMs), the incidence is even higher, particularly after bleeding or surgical treatment. After ruptured aneurysms, subarachnoid hemorrhage can be rather severe

A prospective study found that if the bleeding was stopped quickly, the patients experienced minimal brain injury and cognitive impairments. A year following injury, a significant proportion of patients had diminished mental flexibility along with abnormalities in psychomotor speed, memory, and visuospatial function. Recoveries were not as great for older participants as for younger ones. Distinctive from the impairment caused by ischemic cerebrovascular accidents, ruptured aneurysms can cause more widespread damage and their effects may not always follow well-defined anatomical or neuropsychological patterns in terms of cognitive abnormalities. The AVM is another, albeit less prevalent, cause of hemorrhagic stroke {Beghi E *et al*., 2020}.

When nonhemorrhagic AVMs have significant cognitive effects, verbal or visuospatial processing is impaired according to the expected lateralized pattern, depending on whether the dominant or nondominant hemisphere was affected by the lesion. There may also be deficits that are usually linked to injury to the hemisphere opposite the AVM. Patients with AVM who underwent radiosurgery showed improved memory and attention as well as preserved performance on follow-up tests up to three years later. Regarding the location, depth, and extent of tissue damage, stroke patients vary greatly from one another. The majority of strokes are unilateral; Deficits in cognition are consequently often lateralized. Speech and language abnormalities are frequent aftereffects of left-sided infarcts. The location and size of the lesion determine their specific makeup. Perceptual and visuospatial impairments are frequently among the most noticeable symptoms associated with lesions on the right side {Kanner AM *et al.*, 2022}.

2. Traumatic brain injury

Traumatic brain injury was the cause of epilepsy in 3–4% of individuals. Posttraumatic epilepsy is roughly 10% likely to occur in individuals with severe head trauma (intracranial mass lesions or unconsciousness for more than 24 hours) who do not have any early seizures. The chance of having epilepsy rises to 36% if there are early seizures during the first week. Subjects with light head injuries (amnesia or loss of consciousness for less than 30 minutes), which account for around 80% of all head injuries in civilian populations, have not been shown to be at higher risk. Patients who have survived severe traumatic brain injuries have a wide spectrum of cognitive dysfunctions, varying in severity {Karoly PJ *et al*., 2021}.

Age has a complicated connection with the two major severity predictors (coma duration and posttraumatic amnesia), with increasing age linked to higher morbidity and mortality. The areas most impacted by brain injuries include memory, attention, and the efficiency and speed of information processing. Extended reaction times during two tests indicated severe divided attention problems. Both the capacity to retrieve information from memory and the capacity to store new information in long-term memory may be impacted. Frontal lobe deficits are frequently the most debilitating because they make it difficult for the patient to use their knowledge and abilities in a fluent, acceptable, or adaptive manner {Perucca P *et al.,*2020}.

Depending on the lesion's location, size, kind, and depth, further cognitive problems could exist. Perceptual and linguistic abilities are typically retained. The detrimental impact of epilepsy on neurobehavioral disorders, such as disinhibited behavior, irritability, and aggressive and agitated behavior, was shown in a large-scale prospective study involving patients with severe brain injury. The increased prevalence of behavioral abnormalities, especially aggressive and agitated conduct, may be explained by the discovery of hypoperfusion of the anterior temporal lobes in epileptic patients compared to individuals without epilepsy.

3. CNS infection

Brain infections are the cause of two to three percent of epilepsies. Infants with epilepsies are frequently caused by this etiology. In the senior population, there is a second peak observed. Viral encephalitides are associated with the highest risk of both acute and chronic epileptic seizures. Temporal lobe involvement is a prominent presenting feature of herpes simplex encephalitis, the most common and severe form of encephalitis. In the acute stage, epileptic signs are rather prevalent {Milligan TA *et al*.,2021}. Herpes simplex encephalitis frequently results in temporal lobe epilepsies. Symptomatic seizures during the acute condition raise the

20-year risk of epilepsy from 10% to 22%. Patients with bacterial meningitis have a roughly five-fold increased risk of developing epilepsy, whereas those with aseptic meningitis do not see any appreciable increase in risk. The 20-year chance of developing epilepsy is 13.4% if the acute illness is exacerbated by seizures, compared to 2.4% if it does not. Particularly among CNS infections, encephalitides are known to seriously impair patients' cognitive function. Individuals who have survived a herpes simplex encephalitis exhibit extremely dense memory deficits with significant retrograde and anterograde amnesia, which corresponds to their brain tissue destruction. Deep alterations in behavior are reported, including hyperorality, a loss of fear, social responsibility, and personal and social inhibitions, as well as a weakened capacity for discrimination. The viral invasion of limbic regions explains these behavioral changes, which are most likely related to amygdala injury {Hauser WA *et al*.,2019}.

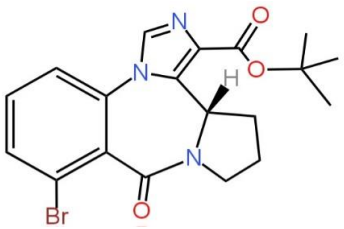
4. Brain tumors

A brain tumor is responsible for 12% of acquired epilepsies and 4% of all occurrences of epilepsy. All ages can experience epilepsy from this cause, however people between the ages of 25 and 64 experience the highest incidence. Ninety percent of oligodendrogliomas (90%) have the highest epileptogenicity, followed by glioblastoma multiforme (34%) meningioma (69%), astrocytomas (69%), and metastatic tumors (41%). Given that frontal lobe tumors are most likely to result in secondary generalized seizures, the location of the tumor may have an impact on epileptogenicity. Most epileptogenic tumors grow slowly and are located close to the rolandic fissure. Brain tumors impair brain function in multiple ways, including hypertension, convulsions, invasion or replacement of brain tissue, hormone secretion, and altered endocrine patterns that impact other bodily systems. Intense cerebral pressure can impair intelligence and result in disorientation and memory problems. Similar to how other distinct brain lesions influence behavior, the tumor's location may have an effect on behavior. The size and growth rate have an impact on the neuropsychological profile in addition to the lesion site. Intracranial tumors often result in reduced adaptive skills, emotional dysregulation, altered personalities, and cognitive deficiencies. The majority of symptoms start out mildly and increase slowly. At the time of diagnosis, the majority of patients with frontal or temporal lobe brain tumors show signs of cognitive impairment. Ninety percent of patients with frontal or temporal lobe brain tumors showed impairment in at least one cognitive domain, such as language, executive processes, memory, or attention. Seventy-eight percent of the patients showed signs of executive function impairment, and over sixty percent showed signs of memory and attention impairment {Asadi-Pooya AA *et al*., 2023}

5. Degenerative CNS disease

About 2 percent of all occurrences of epilepsy are linked to a degenerative process. As people age, degenerative brain diseases become more common. Less than 1% of people 65 to 69 years old have Alzheimer's disease, while the number of patients who are affected by the disease can rise to 8% in those over 85. An key risk factor for new-onset seizures in older persons is advanced Alzheimer's disease alone. Epilepsy risk increases by ten times in people with Alzheimer's disease. There was no clinical evidence linking the generalized tonic-clonic seizures that were observed to any epileptogenic variables other than Alzheimer's disease. The most noticeable of the early signs of Alzheimer's disease is memory loss. Impaired short-term memory and poor long-term learning and memory retention are the initial signs. Memory storage and retrieval impairment is indicated by the poor learning and intrusive errors. Moreover, deficiencies in visuoperceptual function are frequent. Alzheimer's patients may perform worse on tests involving visual discrimination, analysis, spatial judgments, and perceptual organization, even though the pattern of dysfunctions can vary greatly. Not all patients have attentional difficulties, especially in the early stages. However, this could be an additional symptom. Attention deficits include shortened attention span, poor concentration and shifting, and slowed choice reaction time have all been documented {Orsini A *et al*.,2018}. At the early stages of the disease, most Alzheimer's patients exhibit deterioration in verbal abilities, including verbal comprehension and speech quality, quantity, and meaning. Patients exhibit deficits in verbal fluency, verbal reasoning, and reading comprehension when assessed formally. Language abilities may show an earlier loss in epileptic Alzheimer's patients than in non-seizures people.

Structure Of Bretazenil

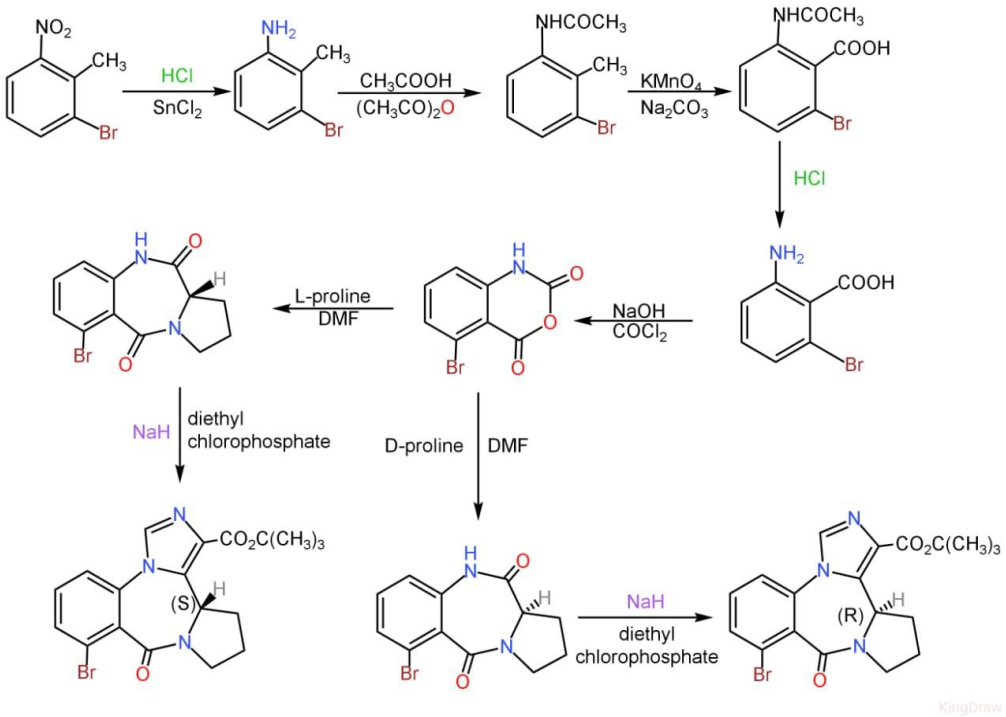


BRETAZENIL

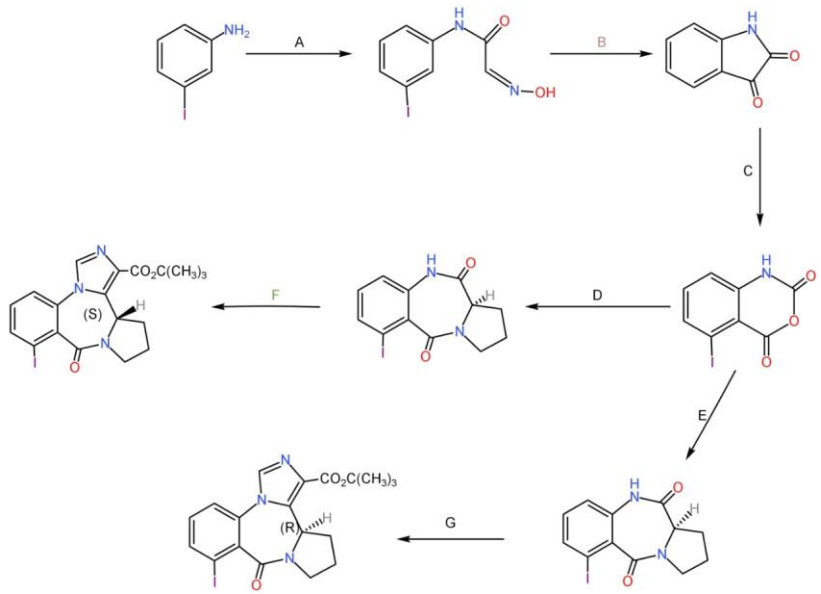
1. Synthesis of Analogues of (S) And (R)-Bretazenil

Increased temperature-induced debromination. Anhydride 14 was created when phosgene (20% solution in toluene) was added to a solution of 13 in NaOH (1M). After crystallization,

the pyrrolobenzodiazepine IS was produced in 60% yield by reacting 14 with 1 equivalent of L-proline in refluxing DMF. The (S)configured enantiomer at C-1I was obtained with the use of L-proline. Likewise, the (R)-configuration at C-l I produced 16 in response to 14's unnatural D-proline reaction {Asadi-Pooya AA *et al*.,2022}.



2. Synthesis of Analogues of (S) And (R)-Iodobretazenil



Reagents A ; CCl_3CHO, NH_2OH-HCI, Na_2SO_4, HCI; **B**: H_2SO_4,95; **C**: CrO_3, $(CH_3CO)_2O$, CH_3COOH; **D;** L-Proline, DMF**; E:** D-proline, DMF; **F:** NaH, diethyl chlorophosphate, tertbutylisocyanoacetate\NaH,-40°C.

MECHANISM OF ACTION OF BRETAZENIL

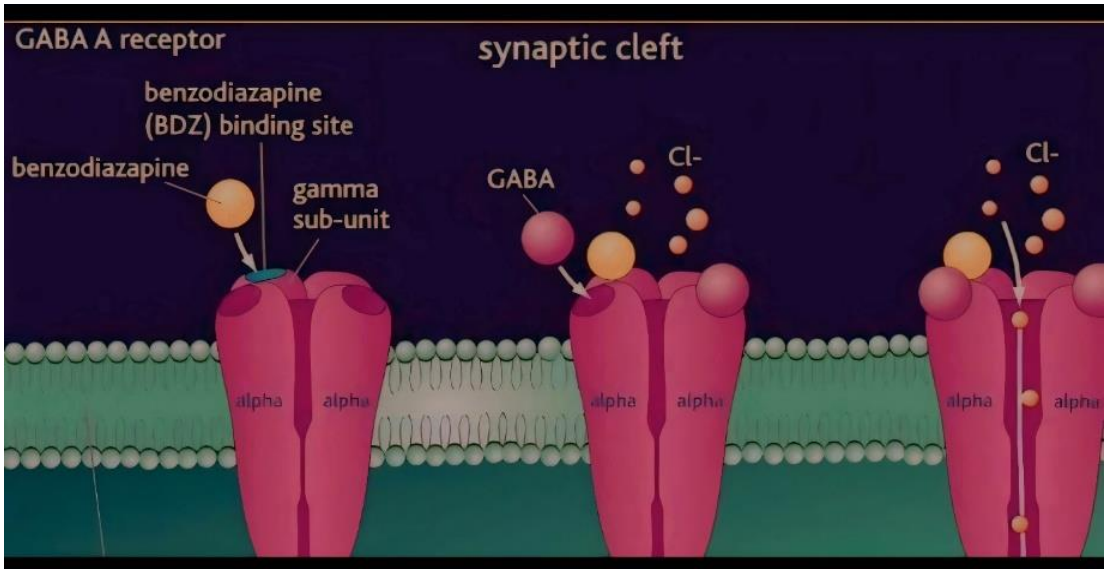
Bretazenil is known to act as a partial agonist at benzodiazepine receptors, specifically the GABA-A receptors in the central nervous system. Benzodiazepines primarily act on the central nervous system by enhancing the effects of the neurotransmitter gamma-aminobutyric acid (GABA) {Kendis H *et al*., 2015}.

GABA Receptors: Benzodiazepines bind to specific sites on the GABA-A receptor, which is a ligand-gated chloride channel.

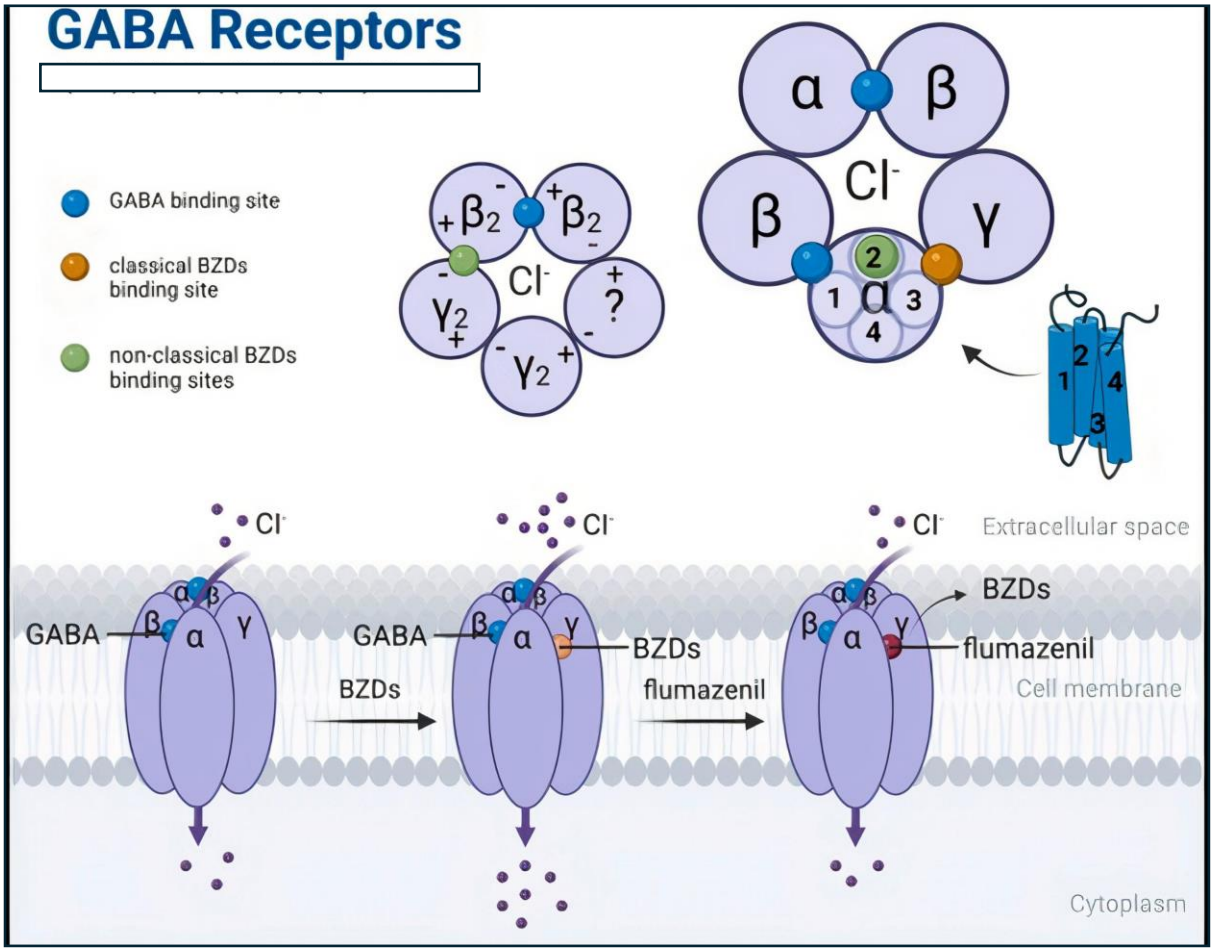
Increased Chloride Conductance: When benzodiazepines bind to these receptors, they increase the frequency of channel opening when GABA is present. This allows more chloride ions to flow into the neuron.

Hyperpolarization: The influx of chloride ions causes hyperpolarization of the neuron, making it less likely to fire an action potential. This inhibitory effect leads to a calming effect on the brain.

Effects: The enhanced GABAergic activity results in anxiolytic (anxiety-reducing), sedative, muscle relaxant, anticonvulsant, and amnesic effects, depending on the specific benzodiazepine and its dosage.



Benzodiazepines are commonly used for anxiety, insomnia, muscle spasms, and seizures, among other conditions. However, their potential for dependence and withdrawal symptoms is an important consideration in their use{ West S *et al*., 2019}.



Bretazenil has also been reported to function as a competitive receptor antagonist, blocking the direct effects of full benzodiazepine receptor agonists in a manner similar to the benzodiazepine receptor antagonist flumazenil. When administered in combination with acute doses of a full benzodiazepine receptor agonist, bretazenil antagonized the effects of the agonist on motor behaviour, shock-suppressed responding, defensive behaviors, and response sequence acquisition and retention. Antagonism of the discriminative stimulus effects of full benzodiazepine receptor agonists has also been reported. Thus, it appears that bretazenil can antagonize both anxiolytic and sedative/myorelaxant effects of a full benzodiazepine receptor agonist. Despite demonstration that partial benzodiazepine receptor agonists antagonize the effects of full benzodiazepine receptor agonist {Falco-Walter J *et al*., 2020}.

Conclusion

The review of Bretazenil's anti-epileptic properties highlights its potential as a promising therapeutic agent in the management of epilepsy. The current evidence suggests that Bretazenil may offer a unique mechanism of action, distinguishing it from other anti-epileptic drugs by targeting specific pathways that modulate neuronal excitability. Its efficacy in preclinical models and early clinical trials demonstrates a favourable profile in reducing seizure frequency and severity, though further research is needed to fully establish its safety and long-term effectiveness.

Future studies should focus on larger clinical trials to validate these findings and elucidate the optimal dosing regimens. Additionally, exploring the pharmacokinetic and pharmacodynamic properties of Bretazenil will be crucial for understanding its full therapeutic potential. Overall, Bretazenil represents a hopeful addition to the arsenal of anti-epileptic therapies, offering potential benefits for patients who are resistant to current treatment options.

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