Benzodiazepine Receptor Antagonists
Possible Uses in the Treatment of Neuropsychiatric Disorders

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Summary

The receptor to which benzodiazepine hypnosedatives and anticonvulsants bind was discovered and characterised in the late 1970s. Agonists and inverse agonists that act at various sites within the receptor complex have been identified. In addition, antagonists of the benzodiazepine receptor have been synthesised. At present, flumazenil is the only agent of this class that is available clinically.

Flumazenil has well documented benefits in the treatment of hepatic encephalopathy and benzodiazepine overdose. The drug has also been studied as a potential treatment for neuropsychiatric illnesses in which dysfunction of the γ-aminobutyric acid (GABA)ergic system is implicated as a causal factor. Potential therapeutic benefits are suggested in benzodiazepine tolerance and withdrawal, benzodiazepine-related amnesia, epilepsy, sleep disorders, cognitive disorders and idiopathic recurrent stupor. In contrast, no clear benefits have been
found in alcoholism, anxiety and movement disorders. Flumazenil induces few adverse effects, and so represents a promising tool for pharmacological investigations of the GABAergic system and for imaging of the benzodiazepine receptor. As an imaging agent it has been used for quantification of the receptor, and as a neuronal marker in epilepsy and cerebral ischaemia.

1. Pharmacology of the Benzodiazepine Receptor

Benzodiazepines interact with the benzodiazepine allosteric modulatory site of the \( \gamma \)-aminobutyric acid (GABA)\(_A\) receptor in the CNS.\(^1\)\(^,\)\(^2\) The GABA\(_A\) receptor is a chloride channel complex that mediates fast inhibitory transmission in the brain. The receptor is composed of 5 protein subunits. 16 different subunits classified in 5 different classes have been described, including 6 \( \alpha \) subunits, 4 \( \beta \) subunits, 3 \( \gamma \) subunits, 2 \( \delta \) subunits and 1 \( \rho \) subunit.\(^3\) Different classes of subunits have 30 to 40% sequence homology with each other, while subunits within one class share 60 to 70% homology. The presence of an \( \alpha \) and a \( \beta \) subunit is necessary for a functional chloride channel and binding of the high affinity GABA\(_A\) agonist muscimol.\(^4\) The \( \gamma \) subunit seems to be essential for a benzodiazepine effect on channel activity.\(^3\)\(^,\)\(^5\) The differential subunit composition confers great heterogeneity to the benzodiazepine receptor, which manifests in a complex regional pharmacology.

Three subtypes of benzodiazepine receptor have been described based on different pharmacological properties. These subtypes correspond to a different subtype composition of the receptor complex:\(^6\)\(^-\)\(^9\)

- Benzodiazepine BZ-I receptors contain predominantly \( \alpha_1 \) subunits and are present throughout the CNS.
- BZ-II receptors contain \( \alpha_2\), \( \alpha_3 \) or \( \alpha_5 \) subunits, and are found in more discreet areas such as the hippocampus, striatum and spinal cord.
- Diazepam-insensitive BZ receptors contain \( \alpha_4 \) or \( \alpha_6 \) subunits, and are found predominantly in the cerebellum.

Benzodiazepine agonists enhance the effects of GABA by increasing the frequency of chloride channel opening, thus hyperpolarising the cell. This manifests clinically as anxiolysis, sedation, amnesia, ataxia, anticonvulsant effects and myorelaxation. Inverse agonists produce opposite effects to GABA\(_A\) agonists. In contrast, benzodiazepine receptor antagonists have no effect on the GABA\(_A\)–chloride channel complex. However, they can antagonise the effects of agonists or inverse agonists, whether these are endogenous substances\(^10\) or pharmacological drugs.

2. Benzodiazepine Receptor Antagonists

Flumazenil, a 1,4-imidazobenzodiazepine, is an antagonist at the central benzodiazepine receptor\(^11\) and was discovered by Hunkeler at Hoffman LaRoche Laboratories in 1981. Other benzodiazepine receptor antagonists have been synthesised (see table I); however, flumazenil is the most widely studied drug with this mechanism of action and is the only one that has been approved for clinical use. This review will focus on flumazenil as a prototype for the class of benzodiazepine receptor antagonists. Flumazenil has received much attention as a treatment of benzodiazepine overdose\(^12\) and in hepatic encephalopathy.\(^13\)\(^,\)\(^14\) Other less established uses for flumazenil in medicine and psychiatry have also been investigated and will be discussed in this review.

2.1 Overview of Flumazenil

2.1.1 Pharmacodynamics

Despite being a benzodiazepine receptor antagonist, weak intrinsic agonist effects of flumazenil have been described in humans by some,\(^15\)\(^-\)\(^17\) but not all, investigators.\(^18\)\(^-\)\(^21\) The drug has similar affinity for most \( \alpha \) subunits of the benzodiazepine receptor, with the exception of the \( \alpha_6 \) subunit, for which it has a lower affinity.\(^6\) Thus, it binds equally to most benzodiazepine receptor subtypes,