Endogenous Benzodiazepine Receptor Ligands
(내인성 benzodiazepine 수용체 효현제)

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The benzodiazepine receptor (BZR) is an important component of the γ-aminobutyric acid (GABA) A receptor complex. Three primary functional classes of compounds interact with the BZR to bidirectionally modulate GABA interactions with its receptor and its associated Cl-channel function. These are: agonists (e.g., diazepam); inverse agonists (e.g., methyl-6,7-dimethoxy-4-ethyl-β-carboline-3-carboxylate); and antagonists (e.g., flumazenil). Since the first description of the "endogenous" BZR ligand, many investigative groups have attempted to identify the "endogenous" BZR ligand. A number of compounds, including 1,4 benzodiazepines, ethyl-β-carboline-3-carboxylate, inosine, and the peptide diazepam binding inhibitor have been proposed to be the natural BZR ligand, which is to say a neurotransmitter or hormone synthesized in situ, released in response to specific physiological signals and interacts with the BZR. While these compounds are active as either agonists or inverse agonists at the BZR, none have been conclusively demonstrated to be the "endogenous" BZR ligand. Nonetheless, the need to isolated 1,4 benzodiazepines for pharmacokinetic purpose as well as the quantitation of potential "endogenous" BZR ligands in a variety of pathological states has led to the development of a number of isolation techniques. Extraction of BZR ligands from tissues has been used for investigations of their role in the pathogenesis of hepatic encephalopathy (HE), stress, coping and depression, memory consolidation, and other neuropathologic states.

1. Endogenous BZR ligands in HE

Single cell recordings from Purkinje neurons revealed and increased sensitivity in HE to the inhibitory effects of BZR agonists. In contrast, neuronal firing action was augmented in cerebella of rabbits with HE but not of control rabbits when flumazenil or other BZR antagonists were added to the perfusion medium. This effects may be explained by the displacement from the GABA A-BZR of BZ-like ligand not present in normal brains. Further CSF from rabbits and from humans with HE contains a substance which binds avidly to BZR. These substances were isolated, characterized and positively identified by gas chromatography-mass spectroscopy as BZs both in brains, sera and CSF of men and experimental animals with liver failure. In rats their
concentration in the brain correlated closely with the degree of neurological impairment. In these drug-free animals and humans the presence of BZs (including diazepam and desmethyldiazepam) can not be explained by exogenous BZ administration.

2. Endogenous BZR ligands in stress, coping and depression

Control over stress protects against many of the deleterious effects of stress exposure. The stress control group showed significant protection against pilocarpin-induced seizures, reductions in [3S]-butylbicyclophosphorothionate(TBPS) binding and 3-fold increase of BZ-like substances in brain in comparison to both yoked-inescapable shock and non-shock controls.

3. Endogenous BZR ligands in memory consolidation.

In rats, amygdala BZ-like immunoreactivity decreased by 29% immediately after the animals step down from the platform of an inhibitory avoidance apparatus and decreased by a further 45% immediately after they receive a training footshock. The immediate post-training intraamygdala injection of the central BZR antagonist flumazenil causes memory facilitation, and that of GABA-A agonist muscimol causes retrograde amnesia.

4. Endogenous BZR ligands in other neuropathological states.

Flumazenil, a benzodiazepine antagonist resolved the episodes and normalized the electroencephalogram of a patient who had recurrent spontaneous episodes of stupor or coma in the absence of toxic, metabolic, or structural brain damage. Radioreceptor binding studies showed the presence of a ligand to the central BZR in plasma and CSF during the episodes.