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Etifoxin, unlike benzodiazepines, potentiate GABA receptors in an α subunit-dependent manner

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Anxiety is a common disorder that affects millions of people every year. To treat it, anxiolytic molecules enhance GABAA receptors, thus increasing central inhibition in the human brain. Benzodiazepine (BZD) molecules have been used for decades to reduce anxiety, but with sedative effects. Their pharmacological profile over GABA receptors is well characterized. The non-benzodiazepine Etifoxin (EFX) also acts with anxiolytic effects but with no undesired neurological effect. However, its precise mechanism is unknown. Here, we combined two-electrode voltage clamp experiments in Xenopus oocytes expressing different GABA receptor subtypes and behavioural experiments on mice to investigate the putative selectivity of EFX for GABA receptors as a function of their stoechiometry. Our data show that EFX exerts its positive modulation in a strictly dependent-manner, acting on α_2 and α_3-containing receptors and without any effect on α4-containing subtypes, and a weak effect on α_5- and α_6-. Contrary to BZD molecules, EFX doesn't rely on the third γorδ subunit to enhance GABA activation. We propose a docking model of EFX on GABA receptors, based on the recently crystallized β3 subunit. These results add to the knowledge of the GABA receptor pharmacology and suggest that EFX is an anxiolytic with anticonvulsive-like effect, with no sedative effects.

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Using a new vinyl sulfone as a promising therapeutic strategy to prevent microglia-mediated inflammation in Alzheimer's disease

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Alzheimer's disease (AD) is the most common neurodegenerative disorder in the elderly, characterized by amyloid-beta (Abeta) peptide deposits and chronic inflammation. Microglia was shown to be activated in the early stage of AD and the alarming High-Mobility Group Box 1 (HMGB1) to mediate neuroinflammation. We aimed to investigate whether vinyl sulfone (VS) with anti-cathepsin S, B and L activity was able to inhibit the expression of HMGB1 and if so, to modulate microglia-related inflammatory signaling pathways. The microglia cell line N9 was incubated with 1 μM Abeta alone or in the presence of 20 μM VS, for 24 h. Cell viability was assessed by propidium iodide staining and neuroinflammation by determining the activity of matrix metalloproteinases (MMPs)-9 and MMP-2, the expression of HMGB1, as well as its toll-like receptor-4 (TLR-4). We additionally evaluated the microRNA (miR)-155 (up-regulated by HMGB1) and miR-146a (up-regulated by IL-1β), which are associated with inflammation. Data showed that Abeta increased microglial necrotic death (1.9-fold, $p<0.01$), MMP-2 and MMP-9 activation (~1.6-fold, $p<0.01$), as well as HMGB1 expression (>2.5-fold, $p<0.01$, protein/mRNA), without causing alteration on the TLR4 protein expression. Abeta induced the expression of miR-155 (1.8-fold, $p<0.05$) and marginally of miR-146 (1.3-fold). Interestingly, VS was able to prevent Abeta-related loss of microglia viability ($p<0.01$) and its immunostimulation, sustaining the values of MMP-2, MMP-9, HMGB1 and miR-155 (all $p<0.05$), including miR-146, at control levels (without Abeta). Our study reveals that VS prevents Abeta-induced microglia dysfunction and inflammation and suggests its therapeutic potential in neuroinflammatory diseases.

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