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Review Article

Flavonoids and Its Role in Central Nervous System (CNS)

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ABSTRACT

In the central nervous system (CNS), several flavonoids bind to the benzodiazepine site of the GABAA receptor (ionotropic receptor). Benzodiazepines are widely prescribed in the class of antipsychotics currently used in treatment, despite the unwanted effects of muscle relaxation, ataxia, amnesia and dementia. Flavonoids have been shown to have a selective effect on the binding site of benzodiazepines in the central nervous system (CNS). Both natural and artificial flavonoids can have multiple effects on the activation of γ-aminobutyric acid (GABA) ionotropic receptors. Flavonoids are known for their medicinal use in the treatment of mental disorders and are also used to study the modulatory sites of the A-type GABA receptor. This ability to influence this function through its effect on GABA receptors enables the many effects of flavonoids, as well as their anxiolytic, sedative, anticonvulsant and analgesic effects.

INTRODUCTION

Flavonoids have been found in nature for almost a billion years, with over 9000 chemical distinct flavonoids known in plant sources. These compounds are low molecular weight substances found entirely in higher plants. There are over 5000 structurally different flavonoids. Flavonoids exhibit a wide range of effects, including anxiolytic effects, sedative effects, antiiconvulsant effects, and analgesic effects. These effects are mediated through a variety of interactions with various receptors and signal systems. One of the most important effects of flavonoids is the inhibitory action of γ-Aminobutyric Acid (GABA). GABA is the main inhibitory neurotransmitter released by up to 40% of neurons in the mammalian brain. GABA acts on two groups of receptors: ionotropic and metabotropic. GABA typeA receptors (Ligand-Gated chloride channels) are ligand-gated chloride channels in the neuron membrane. Once activated by a neurotransmitter These channels allow chloride ions to pass through their chemical gradient. In some cases, chloride ions enter the inward flow of

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these channels and inhibit the firing of neurons. This review will focus on flavonoids and their effects on GABA type A receptors in the central nervous system.

Gabaa Ionotropic Benzodiazepine Receptor

GABA is a neurotransmitter in the central nervous system of the human body. It plays a major role in the regulation of seizures, sedation, and anxiety and works by binding to GABA receptors. Heteromeric GABA receptors allow for the passage of associate degree influxes of chloride ions, thereby reducing depolarization of an excitatory input, thereby reducing excitability. Consequently, the cell is pre-occupied and anticonvulsive, sedative, or anxiety-like activity is produced. The type of activity depends on the type of receptor. There are 5 subunits of GABAA, composed of two alpha subunits, two beta subunits, and a subunit of either γ (γ) or δ (δ). In addition to the binding site of the neurotransmitter itself, these are regulatory binding sites on the receptor. Benzodiapines bind to the putative benzodiazepine site regardless of where they modulate the receptor to become more sensitive to GABA, thus producing anticonvulsant, sedative or anxiolytic effects.[4].

Flavonoids And Benzodiazepines: -

Flavonoids were first associated with benzodiazepines when S-(-)-equol, 4-hydroxy-7-methoxyisoflavone, and 3',7-dihydroxyisoflavone isolated from bovine urine inhibit benzodiazepine binding to the meninges.[5] When flavonoids were prepared for GABA receptors during the initial analysis, benzodiazepines were among the most popular recipes, and several classes of flavonoids were investigated both in vitro and in vivo for their potential to lead to new benzodiazepines. to the website. Ligands.[6]

Flavonoids can act on GABAA receptors through the classical benzodiazepine binding site and independently of classical benzodiazepine binding sites.[7] Several flavonoids induce two-step reactions that increase GABA activity at low concentrations and inhibit it at high concentrations. In addition, some flavonoids act as agonists, especially at high concentrations, and bind directly to receptors in the absence of GABA.[3] Therefore, it is clear that flavonoids interact with at least two and accessible specific active sites on GABAA receptors.

Types of Flavonoids

Flavonoids kind a class of molecules that consists of a benzopyran moiety (A and C rings) with a phenyl substitute (B ring), as shown in fig 1

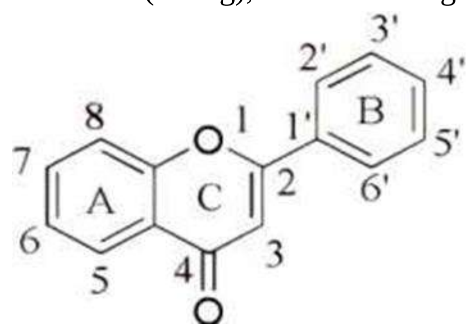

Figure 1: Structure of flavonoids with numbering system and ring designation.

The degree of oxidation of the C ring, the hydroxylation pattern of the C ring structure and the substitute in the 3-position demarcate the different subgroups of flavonoids. The predominant subgroups of naturally occuring flavonoids include flavonols(e.g. quercetin), flavone (e.g. Apigenin, luteolin), isoflavones (e.g. genistein), flavanones (e.g. naringenin) anf flavols (e.g. epigalocatechin gallate (EGCG). Each of the flavonoids listed is known to influence $GABA_A$ receptors and to produce CNS effects.[3

Natural Flavonoids As Ionotropic ($GABA_A$) Receptor Ligands

Nature dispenses science and society with nearly unlimited lay out of structurally various and biologically active molecules. Some of them are directly useful for industrial applications, while others are useful for studying and understanding biological phenomena at the molecular level. Flavonoids are only a moderate example.[1] Apigenin, a type of flavonoid derived from flavones, shows that the main flavonoid in Luffa Acutangula has complex modulatory effects on GABAA receptors.[8] Apigenin competitively binds to the benzodiazepine binding site of the GABA type A (ionotropic receptor) and has significant anxiolytic activity in mice. However, in other studies in rats, apigenin was found to have a sedative effect.

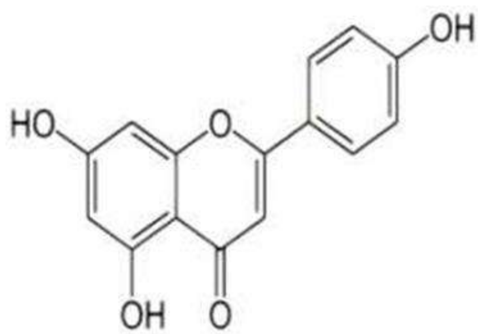

Figure 2: Apigenin (flavones) type of flavonoids.

Flavonoids In Neurodegeneration: -

According to scientific studies, flavonoids affect memory, cognition and neurodegeneration. However, several studies have been conducted in this field with flavonoid-rich fruits. Both studies show that flavonoids have potential value in protecting neurons from damage caused by neurotoxins and neuroinflammation, the ability to activate junctional signaling, and the ability to improve cerebral blood flow. Studies with fruit supplements show that flavanols, flavanones and anthocyanidins improve memory. This indicates that flavonoids, which have effects through signaling pathways, are involved in the memory process, but the exact mechanism of action has not been elucidated. Flavonoids can affect epithelial tissue functions and peripheral circulation. Therefore, they can be useful in the prevention of cerebrovascular disorders, but the effects of flavonoids have not been sufficiently studied. Various flavonoids have been shown to protect against nerve cell damage. Epicatechin, 3'-O-methyl-epicatechin and hesperetin protected neurons against oxidative neuronal damage. Flavanonarigenin was able to prevent the inflammatory process that causes nerve cell damage. Flavonol-quercetin, and thus flavan-3-ols-catechin and epigallocatechin-gallate, also influence neuroinflammation.[4]

Flavonoids Permeability Across The Blood Breain Barrier (Bbb}

The blood-brain barrier (BBB) is mainly formed by the epithelial cells of the brain capillaries, but other cell types such as pericytes, astrocytes and neurons also play an important role. Brain capillary epithelial cells differ from peripheral epithelial cells in that brain epithelial cells have tight junctions that prevent the extracellular transport of small and large water-soluble compounds from the blood to the brain. Transcellular transport has low vesicular transport and high metabolic activity. In general, the blood-brain barrier acts as a physical and metabolic barrier. The ability of flavonoids and their conjugates to cross the BBB and reach the central nervous system is a prerequisite for the functioning of the central nervous system[4].

Functions And Applications Of Flavonoids

Flavonoids protect the functions of the physical body. Flavonoids are analogues and have a wide range of health-enhancing effects. They are an important part of extreme nutritional, pharmaceutical, medical and cosmetic applications. This is often related to their antioxidant, anti-inflammatory, mutagenic and carcinogenic properties, which are related to their ability to modulate the basic functions of cellular proteins. Flavonoids act as antioxidants, antimicrobial agents, photoreceptors, visuals, attractants, nutritional barriers and light screens in plants. Several studies have shown that flavonoids have biological effects, including anti-allergic, anti-viral, anti-inflammatory and dilator effects. However, the greatest interest is devoted to the antioxidant effect of flavonoids, because they can reduce the formation of radicals. Flavonoids promote the production of metabolizing proteins such as glutathione S-transferase, quinone reductase and uridine-5-diphosphate-glucuronyltransferase, during which carcinogens are detoxified and thus removed from the body. Flavonoids are therefore of interest as drugs in medicine and, similarly, as pesticides in agriculture. Flavonoids have been shown to be very effective in prevention lipoid peroxidation and lipoid peroxidation are the cause of several diseases such as atherosclerosis, diabetes, antimicrobial agents, hepatotoxicity and inflammation, and aging. Flavonoids influence the replication and infectivity of specific RNA and DNA viruses. Flavonoids and their effects on central nervous system protection raise concerns about neurodegenerative disorders caused by the combination of oxidative stress and transition metal accumulation.[9].

CONCLUSION: -

Since flavonoids were first connected to benzodiazepines binding sites on $GABA_A$ receptor few years ago, recent studies have clearly indicates that the actions of flavonoids on these receptors are far more compounded than a single action at a single site and also flavonoids are leading drug in the treatment of mental disorder, can be used as tools to study modulatory sites at $GABA_A$ receptor and to develop GABA subtype selective agents further.

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