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Flavonoids and Its Role in Central Nervous System (CNS).

Monika R Gawle [1*], DR. R J Mandade [2]

[*1] M.Pharm Student, Department of Pharmacology, S N Institute of Pharmacy,Yavatmal, India.
[2] Professor and Head of Department, Department of Pharmacology, S N Institute of Pharmacy,Yavatmal, India.

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ABSTRACT: In the Central Nervous System (CNS) several flavonoids binds to the Benzodiazepines site on $GABA_A$ receptor (ionotropic receptor). Benzodiazepines have been widely prescribed category of psychotic medication in current therapeutic use, despite the unwanted aspect effects that produces myorelaxation, ataxia, amnesia, dementia. Flavonoids are shown to possess selective effinity for the benzodiazepines binding site in Central Nervous System(CNS). Flavonoid naturally and artificially both are well-known to be have numerous effects on the activation of ionotropic receptors for γ-aminobutyric acid (GABA). Flavonoids are well-known medication use within the treatment of mental disorders, and also be utilized to study modulatory sites at GABA type A receptor. This ability to influence perform via their actions on GABA receptors permits a variety of effects of flavonoids as well as relief of anxiety, sedative, anticonvulsant and analgesic actions.

KEYWORDS: Flavonoids, CNS, Apigenin, $GABA_A$ Receptor, ionotropic Receptor.

I. INTRODUCTION:

Flavonoids may have existed in nature for nearly one billion years, over 9000 with chemical distinctive flavonoids are known in plants sources.[1] These compounds have low molecular weight substances, found altogether in higher plants. Over 5000 structurally distinct flavonoids are represented.[2] Flavonoids have shown a variety of effects, like anxiolytic, sedative, anticonvulsant and analgesic properties via their actions on the central nervous system (CNS). These effects occur through a range of interactions with different receptors and signal systems, including γ-Aminobutyric acid (GABA) is that the primary inhibitory neurotransmitter in the mammalian brain, discharged upto 40% of neurons. GABA acts on two classes of receptor-ionotropic and metabotropic. GABA typeA receptors are ligand-gated chloride channels located in the neuronal membrane. Once activated by neurotransmitter, these channels permits the passage of chloride ions down their chemical gradient. Sometimes endsup in the inward flow of chloride ions and the inhibition of neuronal firing.[3] The present review is focus on the actions of flavonoids on the central nervous system, more precisely their effect on gamma amino butyric acid (GABA) type A receptors.

II. $GABA_A$ IONOTROPIC BENZODIAZEPINE RECEPTOR:

GABA is the vital inhibitory neurotransmitters in the human central nervous system. GABA has huge involment in epilepsy, sedation and anxiolysis and works via binding to $GABA_A$ receptors. $GABA_A$ receptor are heteromeric GABA, which allows to pass associate degree inflow of chloride ions. This leads to a decrease of the depolarizing effects of an excitory input, thereby depressing excitability. As a result the cell is reserved and an anticonvulsant, sedation or anxiolytic activity is obtained. These type of activity is depends on the subtype of the receptor. The $GABA_A$ receptor consists of 5 subunits, made up of two α, two β, and one γ or δ subunit. Various isoforms exists (α1-α6, β1-β3, γ1-γ3,δ), certainly giving a huge number of combinational mixes. However, only 10 subunits combinations make up the physiologically relevant $GABA_A$ receptor in the brain.

Besides the binding site for the neourotransmitter itself, they are regulatory binding sites on the receptor. Benzodiapines bind to the alleged benzodiazepines site, wherever they modulate the receptor to be a lot delicate to GABA, and thereby yiedling anticonvulsant, sedative or anxiolytic impact.[4]

III. FLAVONOIDS AND BENZODIAZEPINES:

Flavonoids were first complex to benzodiazepines when S-(-)-equol, 4-hydroxy-7-methoxyisoflavone and 3',7-dihydroxyisoflavone, isolated from bovine urine, were shown to inhibit benzodiazepines binding to brain membrane.[5] At

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the time of initial analysis into flavonoids at GABA receptors, benzodiazepines were amongst the foremost wide prescribed pharmaceutical, and various flavonoids of the several classes were investigated both in vitro and in vivo as potential leads for novel benzodiazepines site ligands.[6]

Flavonoids can influence $GABA_A$ receptors via the classical benzodiazepines-binding site, as well as independently of the classical benzodiazepines-binding sites.[7] Several flavonoids elicit biphasic reponses, enhancing GABA actions at low concentration and inhibiting at high concentrations. In addition some of flavonoids act as agonists particularly at high concentrations and directly get the receptors in the absence of GABA.[3] Clearly then, flavonoids interact with atleast two, and attainable more particular active sites on $GABA_A$ receptors.

IV. 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

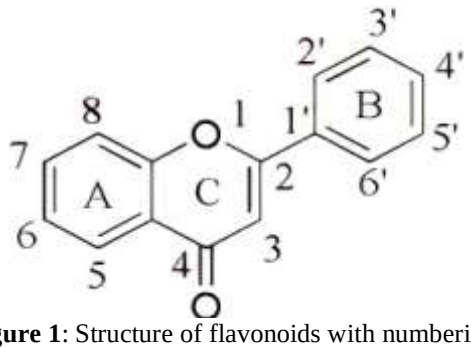

Figure 1: Structure of flavonoids with numbering system and ring designation.

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]

V. NATURAL FLAVONOIDS AS IONOTROPIC ($GABA_A$) RECEPTOR LIGANDS:

Nature dispense science and society with nearly unlimited lay out of structurally various and biologically active molecules. Wheareas some are directly helpful in industrial applications, others are valuable for learning and understanding biological phenomena at the molecular level. Flavonoids are only a moderate example.[1]

Apigenin from flavones sort of flavonoids is that the major flavonoid found in Luffa Acutangula has complex modulatory actions on $GABA_A$ receptor.[8] Apigenin competitively binds to the benzodiazepines binding site of the GABA type A (ionotropic receptor), has clear anxiolytic activity in mice. However, other studies performed in rats found that apigenin has sedative activity.[1]

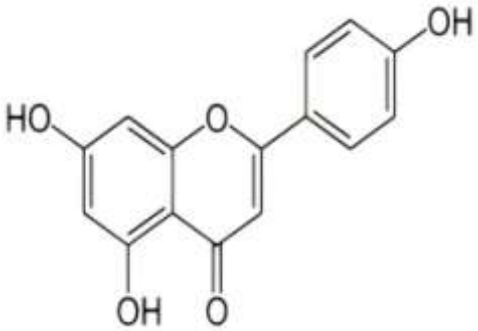

Figure 2: Apigenin (flavones) type of flavonoids.

VI. FLAVONOIDS IN NEURODEGENERATION:

As per scientific survey shows that flavonoids have effect on memory, cognition and neurodegeneration. However, several of the studies during this field are performed with flavonoid rich in fruits, both these studies shows that flavonoids have potential value to gaurd neurons against injury evoked by neurotoxins and neuroinflammation, a possible to activate junction signalling and an capability to reinforce cerebrosvascular blood flow.

Studies with the fruit supplements indicates that flavanols, flavanones and anthocyanidins have the potency to reinforce memory. It shows that the flavonoids possesing their action via influencing signalling pathways concern with the memory process, but the precise mechanism of action has not been elucitated. Flavonoids are known to affect epithelial tissue functions and peripheral blood flow. Within an equivalent, they could be useful in prevention of cerebrosvascular problems, but the result of the flavonoids is not well investigated. Various flavonoids are shown to protect against neuronal injury. Epicatechin, 3'-O-methyl-epicatechin and hesperetin protected neurons against oxidative neuronal damage. The flavanone arigenin was

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ready to inhibit inflammatory method leading to neuronal cell injury. The flavonol quercetin and therefore the flavan-3-ols catechin and epigallocatechin gallate also have an affect on neuroinflammation.[4]

VII. FLAVONOIDS PERMEABILITY ACROSS THE BLOOD BREAIN BARRIER (BBB):

The blood brain barrier (BBB) is particularly shaped by brain capillary epithelium cells, however additional cell types like pericytes, astrocytes and neuronal cells also plays an vital role. Brain capillary epithelial cells differ from peripheral epithelial cells as brain epithelial cells have tight junctions that stops paracellular transport of little and enormous water soluble compounds from blood to the brain. Transcellular transport have low vesicular transport and high metabolic activity. Altogether, the Blood Brain Barrier functions as a physical and metabolic barrier. A prerequitsite for CNS activity is thus that flavonoids and their conjugates are able to tranverse the BBB and enter the CNS.[4]

VIII. FUNCTIONS AND APPLICATIONS OF FLAVONOIDS:

Flavonoids perform a spread of protecting the functions within the physical body. Flavonoids are anologous with a broad spectrum of health upgrade effects. They are an important part in an exceedingly type of nutraceutical, pharmaceutical, medicinal and cosmetic applications. This is often assign to their antioxidant, anti-inflammatory, anti-mutagenic and anti-carcinogenic properties accompany with their capability to modulate key cellular protein functions. Flavonoids act in plants as antioxidant, antimicrobial, photoreceptor, visual, attractors, feeding repellents, and for light weight screening. Several studies have indicates that flavonoids manifest biological activities, including anti-allergic, antiviral, anti-inflammatory medicament and dilation actions.Although, most interest has been dedicated to the antioxidant activity of flavonoids by virtue to their ability to decrease radical formation. Flavonoids faciliates within the manufacturing of metabolising protein like gluthione-S-transferase, quinone reductase and uridine 5-diphosphate-glucuronyl transferase during which carcinogens are detoxified and so abolish from the body. Flavonoids are therefore of interest in drugs as medicinal and at the equivalent case use in agriculature as pesticides. Flavonoids are found to be terribly effective in preventing lipoid peroxidation and lipoid peroxidation is incharge of several disease like atherscleros is, diabetes, antimicrobial, hepatotoxicity and inflammation, along with ageing. Flavonoids have an effect on replication and infectivity of precise RNA and DNA viruses. Flavonoids and their impact on protection of the central nervous system are anxious certain with those associated with neurodegenarative disorder caused by the combined effect of oxidative stress and transition metal accumulation.[9]

IX. 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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