An overview of cognitive aspects of β-carbolines

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ABSTRACT

Mind-altering drugs, especially plants, have fascinated human and always occupied man's attention .Among the plants used by humans, those able to alter the mind and the mood have drawn special consideration. Actually, due to their amazing effects, these drugs, have occupied much of the researchers' time and efforts towards attempts to understand their mechanism, and, hence, to understand human thoughts, behavior, cognitive aspects, sensations and etc. The fact is plants could have beneficial properties to treat mental disease and have some effects on cognitive function. Now we know that plants by originating directly from nature are not less toxic than synthetic drugs. The manner of poisoning with plants can be divided into unintentional or intentional ingestion of plant material and substance abuse. This review article deals with β-carboline, which has effect on CNS.

Keywords: Harmane; Dopamine; Cognitive

INTRODUCTION

β-carbolineis a part of the indole alkaloidsgroup, and it'spyridine ring is fused to an indole skeleton. The structure of β-carbolineis similar to tryptamine[1]. A number of tremorogenic β-carboline alkaloids for example harmane (HA; 1-methyl-β-carboline), 9H-pyrido [3, 4-β] indole (norharmane) and Harmine (7-methoxy-1-methyl-9H-pyrido[3, 4-b]indole)are present in the food chain(figure 1). They have been found in plant-derived beverages, common plant-derived foodstuffs (rice, wheat, corn, mushrooms, barley, soybeans, vinegarand grapes), and plant-derived inhaled substances such as tobacco[2].The β-carbolines harmane, norharmane and harmine, first isolated in Peganum harmala, and related alkaloids are distributed in medicinal plants and exist inmammalian brain tissue, liver, blood plasma, heart andkidney. Since, high plasma levels of these compounds can befound in substance abusers and in some diseasessuch as Parkinson, they are assumed to have a role in the pathophysiologyof different typesof CNS disorders. β-carbolinesnot only have some effects on CNS, but also on some other organs in the humans.So they exhibit variety of psychopharmacological, biochemical, and behavioral effects in animals and humans.For exampleharmine(7-methoxy-1-methyl-9H-pyrido[3, 4-b]indole)which is a tricyclic β-carbolinealkaloid, hasmany traditional and pharmacological uses such as antimicrobial, anti-HIV and antiparasitic affects.

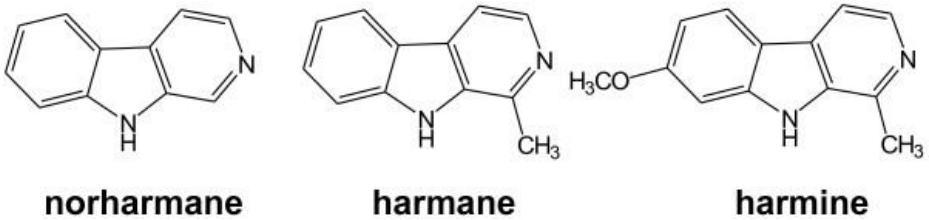

Figure 1. Schematic representation of the chemical structure of 9H-pyrido [3, 4-β] indole (norharmane), HA; 1-methyl-β-carboline (harmane), and 7-methoxy-1-methyl-9H-pyrido[3, 4-b]indole (harmine)

Behavioral effects of harmine in rodents have been investigated. Effect of harmine on animal behavior was assessed in the forced swimming and open-field tests, and the results showed harmine reduced immobility time and increased climbing and swimming time, compared to saline group. Harmine showed beneficial effects on naloxone-precipitated morphine withdrawal syndrome in morphine-dependent rats. Harmine stimulates the central nervous system by inhibiting the metabolism of amine neurotransmitters .Harmine stimulates dopamine release, provingits usagein the treatment of brain disorders.

Neurotransmitters are endogenous chemicals that transmit signals from a neuron to a target cell across a synapse, such as Dopamine, GABA andSerotonin.The β-carbolines havebeen shown to bind to a variety of different targets including monoamine oxidase A and B (MAOA and MAOB), benzodiazepine, imidazoline, dopamine, histamine (under publication) and5-hydroxytryptamine (5-HT) receptors[3, 4].

Following monoamine oxidase (MAO) A or B inhibition β-carbolines increase the level of monoamines[5].Also theyincrease the extracellular dopamine, norepinephrine, and 5-HT levels in differentbrain regions via inhibition of monoamine reuptake[6].As described above biochemical studies have revealed β -carbolines' several actions, for instancebinding to benzodiazepine and opiate receptors inhibition ofMAO_A, competitive inhibition of 5-HT uptake, general inhibition of Na+ dependent transports and action on dopamine receptors, which may participate in a changeable degree in the actions of different types of β-carbolines.

Effect on Seizures

Benzodiazepines and $GABA_A$ receptor agonists have a well-known anticonvulsive effect and are routinely used for antiepileptic treatment, while inverse agonist β -carbolines are convulsant or proconvulsant agents. β-carbolinesact on the benzodiazepine site of the $GABA_A$ receptor. Some of them, such as harmalinehave a systematic agonist action, something likethe action of benzodiazepine agonists.

The others have an inverse agonist action[7].These inverse agonist β-carbolines are important for analyzing the involvement of the $GABA_A$ receptor complexin many behavioral conditions. For example, methyl-6, 7-dimethoxy-4-ethyl-beta-carboline-3-carboxylate (DMCM)is a powerful convulsant[8].Others, called "proconvulsants", produce no spontaneous convulsive effect, but potentiate seizures induced by other compounds [9]. This effect has been studiedwithmethyl β-carboline -3-carboxylate (β -CCM), which is convulsive or proconvulsive in rats[10]and mice [11]. The effects can be compensatedbyan antagonist, such as flumazenil. On the other hand, in some studies, flumazenil at very low doses has seen to potentiate the anticonvulsive effect of benzodiazepines, which means that it has a partial agonist effect.Betweenthe different inverse agonist β-carbolines, β-CCM is usually used for experimental research.

Effect on Anxiety

Anxiety defined as the response of a subject to afulmination that may impair the homeostasis. This canincludetwo parameters: physiological (increase in blood pressure, heart rate,…) or behavioral (inhibition of ongoing behaviors, scanning, avoidance of the source of danger, ...). Benzodiazepines haveanxiolytic effects in both humans[12] and animals[13].β-carbolinesproduce anxiogenic effects in humans and animals. Human studies[14], found evidence of an anxiogenic effect ofsome β-carbolinein healthy volunteers. Also animal studies have demonstratedthat someβ-carbolineshave an anxiogenic effect on rodents[15].β-carbolinesbind with high affinity to benzodiazepine site of the$GABA_A$ receptors as inverse agonists; some possess anxiogenic character and others act asanxiolytic, depending on the dose [16]. In comparison, it should be mentioned that convulsants not acting on the benzodiazepine site, e.g., picrotoxin, have clear anxiogenic effects on mice[17], at doses lower than convulsive doses.So we can understand thatthe efficient dose for producing anxiogenic effects is lower than the dose required for inducing convulsions.

Effect on depression

As we mentioned above β-carbolines bind to other neurotransmitter receptors in the brain,

including 5-hydroxytryptamine (5-HT), dopamine receptors also imipramine/citalopram recognition site [18].Also we know that thesealkaloids increase the extracellular norepinephrine, dopamine and 5-HT levels in several brain regions with inhibitory effect on monoamine reuptake systems.These increase the levels of monoamines after monoamine oxidase (MAO)A or B inhibition.These results suggest a possible role of β-carbolines in control of depression. The β-carbolines harmane, norharmane and harmine which are present in the brain, may be synthesized by condensation reaction of tryptamine with acetaldehyde or pyruvic acid [19].Behavioral effectsof β-carbolines and benzodiazepines are antagonized by flumazenil[20].One study shows that, flumazenil at a dose ineffective per se on the duration of immobility, antagonized the antidepressant-like effects of β-carbolines.It provides some evidence that β-carbolines induce an antidepressant-like effect through stimulation of the benzodiazepine receptor in an inverse way[21]. β-carbolines also display high affinity for I_2-imidazoline receptors [22].These receptors hasbeen implicated in depression[23]. In depression, the levels of I_2-imidazoline binding sites are changed. The antidepressant-like effects of the I_2-ligands have been reported in the animal forced swim test. In conclusion, β-carbolines harmane, norharmane and harmine have an antidepressant-like effect in the forced swim test. This effect seems to be induced by an inverse-agonistic mechanism located in the benzodiazepine receptors.

Effect on Memory

Memory is the process in which information is encoded, stored, and retrieved. Encoding allows information to reach our senses in the forms of chemical and physical stimuli.Storage is maintaining theinformation over periods of time. Finally the third process is the retrieval of theinformation that has been stored.Benzodiazepines are often said to have "amnesic" effects in humans. It hasbeen reported that benzodiazepines induced marked anterograde amnesia after injection [24]. Sincethen, several amnesic effects of benzodiazepines have been describedin humans and animals. However, in different learning situations[25-27][28, 29]flumazenil has effects similar to the effects of an inverse agonist.

β-carbolines, such as DMCM, have been shown to modify learning abilities in animals[30, 31] "Paradoxical" memory-enhancing effects ofβ-carbolines have also been reported in some cases.Some researchers [26, 32] found that direct intracerebral injection of β -CCM (at extremely low doses: 3 μg/0.5 μl) injected into the nucleus basalismagnocellularis of the rat enhanced recognition in a two-trial recognition task. The nucleus basalismagnocellularis of the rat is the equivalent of the nucleus basalis of Meynert in humans, which has an important role in amnesic impairments observed in Alzheimer-type senile dementia[33].The role ofGABAergic neurons in this region, being involved in memory processes, offers new evidence for the designation of GABA in Alzheimer's disease.

Benzodiazepines andβ -CCM appear to act specifically on theacquisition (learning) phase of memory processing. There should be a physiological link between β -CCM–induced convulsions, β -CCM–induced anxious behavior, and β -CCM–induced learning processes, as β -CCM, is convulsant at high doses, anxiogenic at moderate doses, and learningenhancing at very low doses.Therefore a link could be required between learning and mild anxiety, indicatingthat the "normal" state of thebrain for optimal learning would be a state of mild anxiety, and when anxiety levels are too high, there would be pathological problem, such asseizure[34].The limbic system, has been shown to be involved in seizuring[35], anxiety[36], and memory processing[37].In fact, these three processes have been associated with GABA receptors subunits. As mentioned before, β-carboline s can act on CNS binding sites [38], for example5HT2 and 5HT1A receptors, imidazoline receptors, and NMDA receptors.β-carbolinesinhibitenzymes such asmonoamine oxidase $_A$ and, and inducible nitric oxide synthaseNOS).β-carbolines are relatedto decrease level of iNOS protein and NOS promoter activities in a concentration-dependent manner[39].Nitric oxide (NO) has an importantrole, as a second messenger, in the central and peripheral nervous systems. It takes part inspecific forms of long-term potentiation and expression[40].

Table 1. Some neurological effects of β-carbolines

Seizures	β-carbolines have convulsant or proconvulsant effects. Some of them , such as DMCM, are powerful convulsants, whereas some other compounds, such as Ro 15-4513 (a partial inverse agonist), FG 7142 and n-butyl beta carboline-3-carboxylate, have no spontaneous convulsive effect, but potentiate seizures induced by other compounds.
Anxiety	β-carbolines have anxiogenic effects in both animals and humans. Animal studying have shown that certain β-carbolines have an anxiogenic affect on monkeys and rodents.Humans studies , found evidence of an anxiogenic effect of FG 7142(β-carbolines) in healthy human volunteers.
Depression	β-carbolines bind to other neurotransmitter receptors in the brain, including 5-hydroxytryptamine (5-HT)and dopamine receptors .Also we know that these alkaloids increase the extracellular norepinephrine, dopamine and 5-HT levels in several brain regions with inhibitory effect on monoamine reuptake systemsThese results suggest a possible role of β-carbolines in control of depression.
Memory	Several β-carbolines have been shown to modify learning abilities in rodents(promnesic effects),but in some studies they bring memory impairment. Benzodiazepines and beta-CCM appear to act specifically on the acquisition (learning) phase of memory processing.

NO is involved in central effects of some drugs like nicotine, morphine, cannabinoid, ethanol, lithium, and histamine.Furthermore, the hippocampus, which has a main role in learning and memory, is obligatory to mediate the expression of passive avoidance learning.Also several studies indicated that NO and harmane[41] are involved in hippocampus-dependent learning and memory. Some neurological effects of β-carbolines are tabulated in table 1.

CONCLUSION

In recent years, attention has been paid to the health promoting activity of plant foods and their active components. Although essential improvements in the quality control have been made, we should be more careful about the optimization of the extraction and separation procedures of these plants. Thus, further studies are needed to explore the hidden potential of β-carbolines in treating various diseases.

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