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MECHANISM OF ACTION AND BIOLOGICAL APPLICATIONS OF ISATIN- AN INDOLE DERIVATIVE- A REVIEW

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ABSTRACT
Isatin itself is an endogenous oxidized indole with a wide spectrum of behavioral and metabolic effects. It has a distinct and discontinuous distribution in the brain, peripheral tissues and body fluids and isatin binding sites are widely distributed also. Its output is increased during stress. Its most potent known in vitro actions are as an antagonist of atrial natriuretic peptide (ANP) function and NO signaling. Are versatile substrates which act as a precursor for large number of pharmacologically active compounds, thus having a significant importance in the synthesis of different heterocyclic compound. Isatin shows variety of biological activities such as antimicrobial, anticancer, antiviral, anticonvulsant, anti-inflammatory and analgesic.

KEYWORDS: Isatin, metabolic effects, antimicrobial, anticancer, antiviral, anticonvulsant, anti-inflammatory and analgesic.

INTRODUCTION

Endogenous compounds are often used as a basis, or structural component, of pharmacological preparations. For example indirubin is the active ingredient of Danggui Longhui Wan, a mixture of plants that is used in traditional Chinese medicine to treat chronic diseases (Hoessel et al 1999) and also individual Chinese medicinal herbs *Isatis indigotica* and *Strobilanthes cusia* (Mak et al 2004).

Peptide signaling system

The natriuretic peptides are a family of related compounds, including atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP). These peptides and their receptors represent an important regulatory system (Anand-Srivastava and Trachte 1993; Potter et al 2006), involved not only in the regulation of fluid homeostasis and blood pressure, but also into regulation of emotional behavior (eg, anxiety and arousal) and in altered stress hormone release and autonomic nervous system activation (Wiedemann et al 2000). Natriuretic peptides interact with three types of membrane receptor. Two of them, natriuretic peptide receptor type A (NPR-A) and natriuretic peptide receptor type B (NPR-B), are transmembrane glycoproteins exhibiting ligand-dependent intrinsic guanylyl cyclase activity (Anand-Srivastava and Trachte 1993; Silberbach and Roberts 2001; Misono 2002; Trachte 2005; Potter et al 2006). ANP and BNP bind preferentially to NPR-A, whereas CNP exhibits much higher affinity for NPR-B. The third receptor, natriuretic peptide receptor type C (NPR-C), lacks the cyclase domain and binds all three peptides. NPRC receptors are coupled to adenylyl cyclase inhibition through inhibitory guanine nucleotide-regulating protein (Anand-Srivastava and Trachte 1993; Silberbach and Roberts 2001; Misono 2002; Trachte 2005; Potter et al 2006). Isatin inhibited [1]ANP binding to guinea pig cerebellar membranes (Glover et al 1995) and the IC_{50} of 0.4 μM is within the lower limit of the physiological range of isatin concentrations (0.3–1.3 μM). ANP and CNP inhibited [3H]isatin-binding to rat brain sections and isolated membrane fractions and the IC_{50} value for the ANP effect (0.2 μM) (Medvedev, Crumeyrolle-Arias et al 2005) was very close to the corresponding effect of isatin on ANP binding. Isatin also inhibited rat brain particulate guanylyl cyclase activity stimulated by ANP and BNP (Medvedev et al 1998). This suggests the involvement of NPR-A. Recently, it has been reported that isatin in situ blocks the effect of ANP on hyperpolarization-activated current in human atrial myocytes involving cyclic GMP signaling (Lonardo et al 2004). The latter provides further experimental evidence for isatin interaction with NPR-A. Isatin administration blocked cyclic GMP excretion under conditions of fluid overload, which is known to induce endogenous ANP release (Medvedev et al 2001). This provides evidence that isatin can antagonise NPR-A signaling in vivo. Indeed perfusion with 10 μM isatin administration aborted the protective

effect of atrial natriuretic peptide administered just prior to reperfusion evaluated by limited infarction in rabbit hearts (Yang et al 2006). Isatin administration has been shown to block cyclic GMP excretion under conditions of fluid overload, which is known to induce endogenous ANP release (Medvedev et al 2001). This provides further evidence that isatin can antagonise NPR-A signaling in vivo. At high concentrations (100 μM) isatin may also inhibit natriuretic peptide signaling associated with NPR-C (Medvedev, Crumeyrolle-Arias et al 2005). This is consistent with isatin inhibition of ANP, BNP and CNP-induced behavioral effects (Bhattacharya et al 1996a, 1996b; Telegdy et al 2000; Pataki et al 2000), because the three major natriuretic peptides only act in common at one type of natriuretic peptide receptor type C, NPR-C (Anand-Srivastava and Trachte 1993; Silberbach and Roberts 2001; Misono et al 2002; Potter et al 2006). Potter et al (2004) have reported that pretreatment with isatin (100 μg bilaterally) abolished the effect of bremazocine, a κ-opioid receptor agonist, causing enhanced total outflow facility by enhancing levels of natriuretic peptide (ANP, BNP, CNP) in aqueous humor. This is further evidence suggesting that isatin antagonizes natriuretic peptide receptors in situ and in vivo.

Biological Function of Isatin

Isatin was identified as major constituent of tribulin, it is a low- molecular-weight inhibitor of Monoamine Oxidase Type-B (MAO-B).[2] If urinary concentration of isatin is increased in patients it is considered as the diagnostic marker of Parkinson's disease and severity of the disease. Isatin plays an important role in the regulation of acetylcholine (Ach) in brain by increasing the level of Dopamine (DA) under stress.[3,4] Tribulin contains metabolites of isatin[5], but physiological and pathological roles of isatin and tribulin are yet not clear. Due to exercise[6] and old age[7] tribulin levels are found to be increased in humans. Tribulin excretion in human is found to behigher in females than males.[8] Tribulin appears to be enhanced in different conditions such as stress, agitation, or anxiety. Thus these observations represents that during the stress, activated catecholamine-synthesizing cells and corticotropin-releasing factor cells involved in isatin production[9] plays central roles in stress responses. Tribulin acts on central benzodiazepine receptors, and hence suggested to be an anxiety-promoting agent.[10] The potency of tribulin as mono amino oxidase (MAO inhibitory) and benzodiazepine-receptor-binding inhibitors isfound to be roughly equal.[11] It is found to be a selective MAO-B inhibitor. At much higher concentrations, it may also inhibit other enzymes, such as alkaline phosphatase.[12] Tribulin is obtained byextraction from the tissue and body fluids with ethyl acetate. It has been suggested that dietary tryptophan can be converted into an indole by the gut flora and then transported to the liver where it is oxidized.

Mode of action of Isatin

Kumar et al.(1988)[13] suggested that isatin inhibits acetylcholine esterase (AChE) activity in rat brain. The physiological role of isatin is to regulate acetylcholine (ACh) levels in the rat brain, the levels of ACh, choline (Ch), and DA in rat tissues after 2 h of administration (50 or 200 mg/kg, i.p.) was further elucidated , according to it ACh and Ch levels in the striatum receiving isatin increased significantly.[104] In other words, at a single dose isatin simultaneously increased the ACh and DA levels in the WKY striatum. In vitrostudy suggests that, isatin induced an approximate 93% inhibition of MAO and a 5% inhibition of AChE in the rat brain which can be concluded as isatin has a higher affinity for MAO than AChE. Isatin administration also increased Ch, an AChE metabolite of ACh, in many brain regions. These results suggested that isatin increased ACh levels not by inhibiting AChE activity but rather by affecting another pathway.[14] It affects the central nervous system. Isatin has been shown to inhibit a number of enzymes in various tissues, such as acid phosphatase[15], alkaline phosphatase, and xanthine oxidase, hyaluronidase [16] as well as MAO. In a variety of tests isatin are found to have antiseizure activity[17], it also enhances the antiseizure action of propranolol[18]; and its physiological effects protect against stress and certain infections. Yuwiler[19] also found that isatin can acts as benzodiazepine blocker. The most potent action of isatin is the inhibition of the atrial natriuretic peptide (ANP) binding to its receptor. Isatin attenuates ANP-stimulated guanylatecyclase activity in the rat brain, heart, and kidney.[20] Recently it was also suggested that the anxiogenic effect of isatin can be explained by its antagonism of ANP. Isatin and derivatives display diverse pharmacological activities. The biological and pharmacological properties of isatin and its derivatives have led to extensive use of these compounds as key intermediates in organic synthesis. Literature surveys reveal that various derivatives of isatin possess diverse activities such as antioxidant and anti-inflammatory[21], antimicrobial[22], antituberculosis[23], anticancer[24], anti-HIV[25], antiviral[26], anticonvulsant[27,28] activities. Isatin is a core constituent of many alkaloids and drugs as well as dyes, pesticides and analytical reagents. Among all these activities anticonvulsant activity of isatin is discussed below briefly.

Anticonvulsant activity of Isatin

Kumar et al.[29] found that a little variation at para position of the phenyl ring having chloro and nitro substituted compounds i.e. 2a and 2brespectively have excellent anticonvulsant activity compared to that of the substitution at any other position. Among the synthesized compounds such as (1b) 3, 4-dihydro-2-(4-nitro phenyl) imidazo(4,5,6), indol and (1c) 2-(4-chloro phenyl) -3, 4-dihydro-imidazo (4,5,6) indole showed excellent anticonvulsant activity. Prakash et al[30] reported Synthesis, characterization and anticonvulsant activity of novel Schiff base of isatin derivatives. They are synthesized by condensation of isatin with different

aromatic aldehydes. All the synthesized compounds screened for anticonvulsant activities against maximal electroshock (MES) and subcutaneous metrazole (ScMet).Among all the synthesized compounds, 3-(4-(3,4,5-trimethoxy benzylideneamino) phenylimino) indoline-2-one showed excellent anticonvulsant activity with lower dose in MES as well as in ScMet methods. Veerasamy et al.[31] reported the Synthesis of 3-cycloalkanone-3. 4-hydroxy-2-oxindoles derivatives where X can be bromo or chloro. These derivatives showed the MES testand PTZ test. Compound 24a was active in PTZ seizurethreshold test (PTZ), thus act as a potential anticonvulsant. Subudhi et al.[32] reported anticonvulsant and antimicrobial activity of Cu (II), Zn (II) and Co (II) complex of isatin 3-Glycine. Isatin and glycine have inhibitory effects on central nervous system and to capitalize these features metal complexes of isatin-3-glycine were prepared and evaluated for anticonvulsant activity. Among them Cu (II) complex were found to be most active .Ragavendran et al.[33] reported the synthesis of N-aryl/alkylidene-4-(1, 3-dioxo-1, 3-dihydro-2H isoindol-2-yl) butanoylhydrazides/butanamides which was further analyzed for anticonvulsant activity. Compounds were ineffective in MES test up to 300 mg/kg. These compounds were found to be more potent when compared to standard drug phenytoin and ethosuximide, and were effective at dose 30 mg/kg. Sridhar et al.[34] reported the Synthesis of 3-(4-chloro-phenylimino)-5-methyl-1, 3-dihydro-indole-2-one. The synthesized compounds were active inMES test and found to be more potent. when compared to standard drug phenytoin and ethosuximide. Among all 23b was found to be most activecompound and showed 87% protection at 100 mg/kg doselevel . Palluotto et al.[35] Synthesize a series of 2-aryl-2, 5 dihydropyridazino[4, 3- b]indol-3(3H) ones among them Some showed potent anticonvulsant activity (Campagna et al. Synthesize a series of a 2-aryl -2, 5-dihydropyridazino [4, 3-b] indol-3(3H) ones among all compounds having X= H, Cl, Br group were found to be potent against pentylenetetrazole (PTZ) and induced seizures in mice . Popp et al[36] studied Comparative anticonvulsant activity of different compounds. They found that 3-hydroxy-3-acetonyloxindole (10 A) have greater anticonvulsant activity than 3-hydroxyl-3-pehenacycloindole (10 B). The compounds 3-acetonyldeneoxindole (11A) and 3-acetophenylideneoxindole (11B) haveless anticonvulsant activity. Another compound 3-cyclohexenonyloxindole (11C) has enhanced activity in MES screen from 300 to100 mg/kg. Thus compound 3-hydroxy-3-cyclohexanonyloxindole (10C) was found to have potent anticonvulsant drug showing activity at 300 mg/kg by body weight in the MES test.Muller et al.[38] were found that oxindole, isatin an NmethylIsatin-3-thiosemicarbazene injected (1/p) in the rat, inhibited monoamine oxides in liver homogenate, Isatin-3-hydrazone was much less effective as an inhibitor, introduction of Br group at the position 5 in certain analogne safforded 5-bromoisatine, 5-bromo-N-methylisatin and 5-bromoisatin-3-hydrazone. The bromo group markedly increased the inhibitory effectiveness of the unsubstituted compound

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