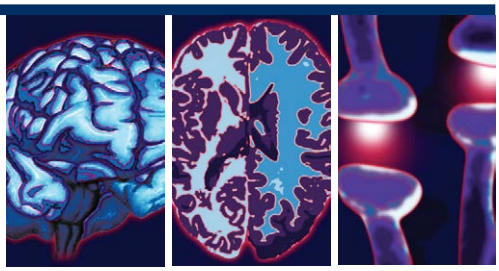
Review



1metiq, an Endogenous Compound Present in the Mammalian Brain Displays Neuroprotective, Antiaddictive and Antidepressant-Like Activity in Animal Models of the Central Nervous System Disorders

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ABSTRACT

Background

The review manuscript raises some important aspects concerning the pharmacology, clinical applications of an endogenous amine, 1-methyl-1,2,3,4-tetrahydroisoquinoline (1MeTIQ), a unsubstituted non-catechol tetrahydroisoquinoline which is present in the mammalian brain. The manuscript is focused on the mechanisms of action of 1MeTIQ in behavioral, neurochemical and molecular studies on rodents. The neuroprotective, antiaddictive and antidepressant properties of 1MeTIQ will be described.

Results

Findings implicate 1MeTIQ in unique and complex mechanisms of neuroprotection in various neurodegenerative diseases of the central nervous system. We believe that MAO inhibition, free radical scavenging properties and antagonism to the glutamatergic system may play an essential role in neuroprotection. At the same time all demonstrated results strongly support the view that 1MeTIQ has a considerable potential as an antidepressant and antiaddictive drug demonstrated in the animal models of depression (forced swim test, tail suspension test, reserpine and clonidine model) and addiction (morphine and cocaine addiction).

Conclusion

Introduced data have shown that therapeutic effects of 1MeTIQ may be coupling with gentle activation of the monoaminergic system (dopaminergic, noradrenergic and serotoninergic) in the brain structures, the simultaneous inhibition of MAO-dependent oxidation and reduction of the glutamate system activity in the brain.

Keywords

1MeTIQ, Mechanism of action, Brain dopamine metabolism, Neuroprotection, Addiction, Antidepressant-like activity, Rat

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Introduction

Tetrahydroisoquinolines (TIQs) are a big family of compounds widespread in plant and animal kingdoms [1,2]. In general, TIQs can be formed by condensation of biogenic amines (phenylethylamines and catecholamines) with aldehydes or α-keto acids in the so-called Pictet-Spengler reaction [1,3], although some of them (e.g. 1-methyl-1,2,3,4-tetrahydroisoquinoline, 1MeTIQ) are also synthesized enzymatically in the mammalian brain [4-6]. Depending on the chemical structure of biogenic amines participating in these reactions, TIQs family can be divided into compounds with catechol and non-catechol structures. The presence of two non-catechol TIQs that is 1MeTIQ and 1BnTIQ, in the brains of humans, monkeys and rodents as well as in the cerebrospinal fluid (CSF) of parkinsonian patients and healthy controls [7-11] has been detected by means of chromatographic methods. 1MeTIQ is considered to be a potential neuroprotective compound, while 1BnTIQ is suspected of displaying neurotoxic properties [12-17]. Interestingly, the amount of 1MeTIQ in parkinsonian patients was reduced and tended to decrease with aging [18]. Additionally, in old rats a 50% reduction in the amount of 1MeTIQ was found in the substantia nigra [8]. As it was demonstrated by others authors 1MeTIQ synthesis is inhibited by different compounds that induce experimental parkinsonism [19,20]. Basing on introduced findings the 1MeTIQ concentration in the brain plays an important role in the pathogenesis of the toxin-induced parkinsonism. What more, the degeneration of the dopaminergic neurons may proceed as a result of the loss of neuroprotection afforded by 1MeTIQ. It is well known that oxidative stress provides a universal mechanism for inducing cell death [21]. In the brain, MOA-mediated deamination of monoamines (especially dopamine) constitutes the main source of toxic ·OH formation and H_2O_2 generation. 1MeTIQ, in contrast to neurotoxic tetrahydroisoquinolines (e.g. salsolinol, 1BnTIQ) **(Figure 1)**, is a reversible inhibitor of MAO A and B activities and possesses antioxidant properties [22]. 1MeTIQ exhibits intrinsic structure-related antioxidant properties, as indicated by the effects of 1MeTIQ on inhibiting free radical formation and abolishing ·OH generation resulting from dopamine oxidation via the Fenton reaction in the abiotic system [16]. In this light 1MeTIQ seems to be an endogenous compound protecting especially dopamine neurons against oxidation stress produced by free radicals. Moreover, 1MeTIQ exists in two stereoisomeric forms, R- and S-enantiomers. Their proportion in the mouse brain amounts to 0.60, implying that 1MeTIQ could be synthesized, at least partially, using an enzymatic pathway [23]. As it was demonstrated in our earlier paper, both stereo enantiomers, similarly to racemate (R,S-1MeTIQ), possess neuroprotective activity against rotenone-induced impairment of dopamine release in the rat brain [24].

Neuroprotection- the effect of 1MeTIQ against rotenone and glutamate-evoked neurotoxicity

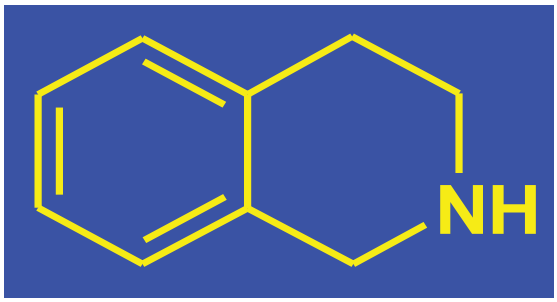
Rotenone, an environmental toxin shows selective neurotoxicity towards dopaminergic neurons [25]. It is a classical, lipophilic inhibitor of mitochondrial complex I, and such mechanism of action was postulated to be the cause of rotenone-induced neurodegeneration [26]. Rotenone also triggers dopamine release, as evidenced by microdialysis and biochemical data [27], and this activity may further contribute to the degeneration of dopaminergic cells. In our study repeated administration of rotenone produced many defects in general behavior of rats, considerable mortality and dramatic increases of dopamine metabolism. One ought to underline that rotenone increased many times dopamine oxidative catabolic pathway and in the same time strongly depressed COMT-dependent methylation and its main product the extracellular dopamine metabolite, 3-methoxytyramine (3-MT). These behavioral and biochemical changes were effectively counteracted by administration of 1MeTIQ before each dose of rotenone [14]. Additionally, rotenone administered intracerebrally to the left medial forebrain bundle (MFB) produced neurodegeneration of dopamine neurons, and also in this case peripheral administration of 1MeTIQ before rotenone, and then during 21 days significantly reduced the fall of striatal dopamine concentration [15]. These data demonstrated that 1MeTIQ is able to counteract the damaging action of rotenone, a dopaminergic neurotoxin, and seems to be a potential neuroprotective agent. Also, our *in vitro* experiments (granular cell cultures obtained from seven day old rats) was found that 1MeTIQ (in concentration-related manner) prevented glutamate-induced cell death and $^{45}Ca^{2+}$ influx [16]. Such profile of 1MeTIQ action suggested specific effects of

this compound on an excitatory amino acid receptor. What is more, 1MeTIQ prevents kainite-induced release of excitatory amino acids from the rat frontal cortex observed in an *in vivo* microdialysis study [16]. The results presented above suggest that 1MeTIQ may exhibit anticonvulsant activity. In fact, 1MeTIQ exerts anticonvulsant effects by increasing the threshold for electro-convulsions and potentiation of the antiseizure action of carbamazepine and valproate against maximal electroshock in rodents [28].

Conclusions: 1MeTIQ offers a unique and complex mechanism of neuroprotection, in which reversible inhibitory effect on monoamine oxidase (MAO A and B), scavenging properties of free radicals, and antagonism to the glutamate-induced excitotoxicity seems to play a very important role.

Addiction

Drug addiction is one of the most difficult medical and social problems, as no effective pharmacotherapy has been available so far. Drug addiction is a chronically relapsing disorder that is characterized by compulsion to take the drug and loss of control in limiting intake. The neurobiological changes that accompany drug addiction have not been understood till now; however, drugs of abuse are unique in terms of their reinforcing properties. Dopaminergic mechanisms are traditional targets in the research into addiction [29-31]. A question arises about the neurobiological substrate of reward. The nucleus accumbens (NAc), as a part of the ventral striatum, as well as dorsal striatum, hippocampus and frontal cortex are considered to be a crucial points of integration of information by receiving emotional and cognitive inputs (frontal cortex, hippocampus), and by projecting to motor output regions (dorsal and ventral striatum) [30]. Early theories on drugs of abuse and natural rewards suggested that activation of dopamine cells in the ventral tegmental area (VTA) and the release of dopamine in target structures signaled reward, especially in the NAc [32,33]. How it was recently demonstrated the glutamate system and its release are also important factors in drug addiction and that imbalance in glutamate homeostasis which is responsible for neuroplasticity may impair communication between the prefrontal cortex and the NAc [34-36].



1,2,3,4-Tetrahydroisoquinoline (TIQ)

1-Methyl-1,2,3,4-tetrahydroisoquinoline (1MeTIQ)

Figure 1: The chemical structures of tetrahydroisoquinolines

Morphine addiction – the effect of 1MeTIQ

Morphine activates opioid μ-receptors and produces the antinociceptive effect called analgesia. In the same time morphine affects the dopamine reward system in the nucleus accumbens leading to the development of morphine addiction [32,37]. As it is well known calcium plays an important role in nociception. Activation of opioid μ-receptors is closely related to the inhibition of calcium uptake and this process is mainly responsible for opioid-induced analgesia [38]. 1MeTIQ co-administered with morphine strongly potentiated its analgesic effect [39-41]. Additionally, as it was demonstrated 1MeTIQ administered before each morphine injection completely inhibited the development of morphine tolerance and prevented naloxone-induced precipitation of the abstinence syndrome: body weight loss and head-twitches in morphine-dependent rats [39]. Moreover, it has been shown that 1MeTIQ is also effective in prevention of morphine-induced place-preference and alcohol intake [42].

A question arises as to the mechanism of action responsible for that clinically interesting effect of 1MeTIQ. As mentioned above, 1MeTIQ

as a neuroprotective substance inhibits the main dopamine oxidative enzyme MAO and simultaneously possesses free radical scavenging properties. 1MeTIQ has also affinity for NMDA receptor as its antagonist and prevents glutamate-induced cell death [16]. Such mechanism of action could be partially responsible for its antinociception and antiaddictive effects [16,43]. Taken together it was demonstrated that complex mechanism of action of 1MeTIQ in the brain leads to its profitable and clinically wanted effects in morphine sensitization and addiction.

Cocaine addiction – the effect of 1MeTIQ

The essential role of the mesolimbic dopaminergic system in addiction has been well established [44,45]. In search of an effective therapy several antidopaminergic drugs were tested as potential anti-abuse agents [46,47]. While neuroleptics have been found not to be useful in that respect, partial agonists of the dopamine D_2 and D_3 receptors offer some hope [48, 49]. Studies of partial agonists with an antidopaminergic profile of action different from that of classical neuroleptics seem justified, and taking into account the data mentioned above, 1MeTIQ is especially an interesting candidate for future clinical studies. In animal studies exogenously administered 1MeTIQ antagonized cocaine-induced locomotor sensitization as well as cocaine self-administration. What is more, 1MeTIQ significantly antagonized cocaine-induced reinstatement of seeking-behavior [50, 51]. Possible anti-abuse properties of 1MeTIQ are particularly interesting, as it has been suggested that this compound acts as a regulator of brain homeostatsis [52-54]. There is a long established view that depression of dopaminergic activity in the limbic structures may be responsible for craving [55,56]. In cocaine-dependent rats administered 1MeTIQ stabilizes dopamine function in the limbic brain structures, and it may be assumed that blockade of reinstatement by 1MeTIQ is related to this effect [57]. Another biochemical action of 1MeTIQ, possibly related to its anticraving effect, may be connected with the activation of the noradrenergic system in the brain. Such effect may be associated with the antagonistic action of 1MeTIQ on alpha-2 adrenergic receptors [58,40,41]. The ability of 1MeTIQ to increase the level of the main metabolite of noradrenaline in the CNS, 3-methoxy4-hydroxyphenylglicol (MHPG), as well as its extraneuronal metabolite, normetanephrine (NM), reflects the antagonistic effect of 1MeTIQ on the alpha-2-adrenoceptors [59].

Conclusions: To explain the mechanism of the antiaddictive effects of 1MeTIQ, its wide spectrum of action in the CNS should be considered. Functional studies have shown that 1MeTIQ acts as an antidopaminergic agent but in contrast to typical neuroleptics, it induces no catalepsy in animals. Moreover, 1MeTIQ is involved in a direct interaction with the agonistic conformation of dopamine receptors and thus acts as partial dopamine agonist. On the other hand, it also displays a moderate effect on the NMDA receptor and the glutaminergic system as well as offers neuroprotection against glutamate-induced excitotoxicity in the rat. The presented results strongly support the view that 1MeTIQ is a compound which has a considerable potential to combat drug addiction, particularly through attenuation of the abstinence syndrome and craving.

Antidepressant-like activity of 1MeTIQ

Recently, depression has been recognized as a major public health problem. Despite intensive research, the etiology and pathogenesis of depression remains unclear. Preclinical and clinical studies suggest that monoamine neurotransmitters: dopamine, noradrenaline and serotonin in the central nervous system play a key role in the pathophysiology of depression [60-63]. These studies have been focused largely on the levels of monoamines and their receptors, and have led to putting forward several theories of depression, including the monoamine depletion and receptor sensitivity hypothesis [61,64,65]. Effective drugs for depression act as MAO inhibitors and/or 5-HT and NA reuptake inhibitors [65-67]. Although a lot of efforts have been invested in the development of new drugs in the last years the situation is still far from satisfactory. To address these needs, antidepressants with a novel mechanism of action and without side effects are in great demand.

1,2,3,4-Tetrahydroisoquinoline (TIQ) and its methyl derivative, 1MeTIQ there are members of tetrahydroisoquinoline family (TIQs). They are the most widespread alkaloids occurring in plants, a variety of food products as well as in the human, primate and rodent brain [1,2,7]. TIQ and 1MeTIQ show high affinity for the brain tissue and easily penetrate into the brain or are actively transported by the organic cation

transporter system [68]. What is particularly interesting, the concentration of TIQs in the brain was several-fold higher than in plasma both after acute and chronic treatment [68]. Additionally, it was demonstrated that TIQ and 1MeTIQ in low micro molar concentrations inhibit enzymatic activity of both isoforms of monoamine oxidase (MAO A and B). Consequently, TIQ and 1MeTIQ inhibit MAO-dependent oxidative deamination of dopamine, the main catabolic pathway leading to the generation of free oxygen radicals [13,69]. In the same time both compounds shift dopamine catabolism towards COMT-dependent O-methylation, what is extremely significant in view of their neuroprotective effects [13, 70]. It is widely known that preclinical and clinical trials are being conducted to evaluate antidepressive potential of several MAO A and MAO B inhibitors and some of them, such as brofaromine and moclobemide are already used as antidepressants [71].

Our latest research have demonstrated antidepressant-like potential of both investigated compounds, TIQ and 1MeTIQ, in behavioral tests involving rodent models of depression [59,72,73]. The behavioral despair tests, like forced swim test (FST) in mice and rats and tail suspension test (TST) in mice, are widely used as useful models for probing pathological mechanism of depression and for evaluation of antidepressant drugs, and possess a high predictive validity for antidepressant efficacy in human depression [74,75]. Recently, a behavioral individual response category was developed including immobility, swimming and climbing [76]. Selective serotonin reuptake inhibitors increase swimming behavior, while drugs acting primarily on elevating extracellular levels of NA or DA increase climbing behavior [77,78]. Clonidine, as alpha2 adrenoceptor agonist, which inhibits release of noradrenaline and suppresses noradrenergic activity was also employed as a useful and well known animal model of depression [79-81]. Another interesting model of depression was obtained by chronic administration of a low dose of reserpine (0.2 mg/kg), which was based on and monoamine depleting action in the brain, and its inhibitory effect on the vesicular monoamine transporter 2 (VMAT2). In fact, behavioral studies have revealed that chronic treatment with a low dose of reserpine induced a distinct depressive-like behavior in the FST as well as significant decrease in the level of dopamine, noradrenaline and serotonin in the rat brain [72]. Reserpine interferes with the storage of monoamines by blocking the ATP-dependent uptake mechanism in the storage organelles [82]. How it was shown by other authors the VMAT2 deficient animals showed progressive loss of dopamine terminals, accumulation of α-synuclein, and an increased oxidative stress, [83,84]. It is important to mention that many studies have indicated that depression is characterized by a significantly decreased antioxidant status, as evidenced by a lowered tryptophan, tyrosine, vitamin E, zinc concentration, and a reduced glutathione level, which are all antioxidants [85-87]. Recently, a new hypothesis was formulated which postulating that the activation of oxidative stress pathways and inflammation may be pathophysiological factors leading to the depression [67,86].

In all of the above introduced animal models of depression, both investigated compounds (TIQ and 1MeTIQ) completely antagonized behavioral and neurochemical syndromes of depressive-like behavior in rodents displaying therapeutic potential similar to a classical antidepressant, imipramine [59,88,89].

Conclusions: Summing up, our studies provide evidence that 1,2,3,4-tetrahydroisoquinoline and its methyl derivative, 1MeTIQ show a potent antidepressant-like effects and their pharmacological activity may be connected with affecting monoaminergic systems (dopamine, noradrenaline and serotonin). Great hopes are placed in the application of 1MeTIQ in antidepressive treatment as a safe drug with clinically useful mechanism of action that has been recently described as a neuroprotectant with antiaddictive potency [72].

Conclusion

1MeTIQ, a compound with high affinity for the brain tissue inhibits the oxidative MAO-dependent dopamine catabolism and activated the COMT-dependent pathway and antagonizes glutamate-induced excitotoxicity such complex mechanism of action of 1MeTIQ may be responsible for its beneficial neuroprotective, antiaddictive and antidepressant-like properties in rodents.

Conflict of Interest

The authors declare no conflict of interest.

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