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Commentary

Methylene blue and Alzheimer's disease

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ABSTRACT

The relationship between methylene blue (MB) and Alzheimer's disease (AD) has recently attracted increasing scientific attention since it has been suggested that MB may slow down the progression of this disease. In fact, MB, in addition to its well characterized inhibitory actions on the cGMP pathway, affects numerous cellular and molecular events closely related to the progression of AD. Currently, MB has been shown to attenuate the formations of amyloid plaques and neurofibrillary tangles, and to partially repair impairments in mitochondrial function and cellular metabolism. Furthermore, various neurotransmitter systems (cholinergic, serotonergic and glutamatergic), believed to play important roles in the pathogenesis of AD and other cognitive disorders, are also influenced by MB. Recent studies suggest that the combination of diverse actions of MB on these cellular functions is likely to mediate potential beneficial effects of MB. This has lead to attempts to develop novel MB-based treatment modalities for AD. In this review article, actions of MB on neurotransmitter systems and multiple cellular and molecular targets are summarized with regard to their relevance to AD.

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1. Introduction

Historically, methylene blue (MB) is the first synthetic compound ever used as an antiseptic in clinical therapy and the first antiseptic dye to be used therapeutically [see 1,2 for reviews]. In fact, the use of MB and its derivatives was widespread in chemotherapy before the advent of sulfonamides and penicillin [see 1 for review]. MB has also been a lead compound in drug research against various bacterial and viral infections [1], and cancer [1,3]. Investigations into its structure and therapeutic activities have played a major role in the development of the phenothiazines [2–4], a large class of drugs employed as antihistamines and neuroleptics.

The beneficial effects of MB in the treatment of cognitive disorders occurring in psychoses have been known for more than a century [5]. Recently, its potential to slow down cognitive decline in Alzheimer's disease (AD) has attracted attention [6–8]. AD is the most common cause of dementia in the elderly. Clinically, it is characterized by progressive cognitive impairment and severe neuropsychiatric disturbances [8,9]. Histopathological hallmarks are extracellular deposits of β-amyloid protein (Aβ, a 40–42-amino acid proteolytic fragment of the amyloid precursor protein, APP) in neuritic plaques, intracellular neurofibrillary tangles caused by the abnormal aggregation of tau protein and neuronal cell loss, particularly affecting the cholinergic system [9].

The present review summarizes the data suggesting that MB is a promising candidate that may help prevent cognitive decline in AD.

2. Biochemical pharmacology

MB, a cationic dye with the chemical name tetramethylthionine chloride, belongs to a class of compounds known as phenothiazines. It is soluble in water and can also dissolve in organic solvents [10]. Its color is deep blue in its oxidized state (MB) with a maximum absorption at light wavelengths of 609 and 668 nm [11], and colorless when reduced to leucoMB, which does not absorb in the visible region. These two forms of the dye exist as a redox couple in equilibrium; together they form a reversible oxidation–reduction system or electron donor–acceptor couple.

In clinical practice, MB is available as a solution (1%, w/v; 10 g/l or 26.74 mM) and the recommended safe dose appears to be between 1 and 4 mg/kg, depending on the source [12]. Typically, MB is administered i.v. or orally (50–300 mg), but interosseous MB

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infusion has also been described [12–14]. In the treatment of methemoglobinemia, it is usually given as 0.1–0.2 ml/kg of a 1% solution administered intravenously (i.v.) over 5–10 min.

In healthy volunteers, mean plasma concentration of 5 μM MB was achieved after i.v. bolus injection of 1.4 mg/kg MB [13]. After oral administration of 100 mg MB, the dose suggested for the oral treatment of methemoglobinemia, whole blood concentrations of up to 25 ng/ml (7–8 μM) were reached in healthy individuals [15]. It is noteworthy that whole blood measurements of MB may not reflect its bio-phase concentrations, since MB binds to blood cells and is extensively taken up by them [16]. Thus, MB concentrations in whole blood have been found to be 4–5-fold higher than in plasma [15,17]. MB also binds to bovine serum albumin with a stoichiometry of 1:1, with the dissociation constant being 2.90 μM [16]. It is estimated that the plasma concentration of free MB is only about 60 nM under the assumption that the total MB concentration is 10 μM, the total albumin concentration is 500 μM and competing ligands of albumin are absent [16]. Thus, not surprisingly, MB has an exceedingly high volume distribution of 21.0 l/kg in rabbits [18]. Interestingly, many of the pharmacokinetic properties of MB show significant dose- and species-dependent variations [15–19].

After oral administration of 100 mg MB, whole blood MB concentrations in healthy individuals were reported to be one order of magnitude lower than after i.v. administration of the same dosage [15]. However, a recent study comparing the administration of single doses of MB (50 mg i.v. versus 500 mg orally) indicated that the absolute bioavailability of MB after oral administration was 72.3% [20]. Reasons for the discrepancies between these studies, such as mode of application (gel capsules versus aqueous oral formulation), blood versus plasma measurements, different methodologies and cellular uptake, have been discussed by the authors [20].

There is strong indication that MB passes the blood–brain barrier [15]. In rats, 60 min after oral administration or i.v. injection, MB concentrations are about 10 times higher in the brain than in plasma [15]. When MB is injected supravitally into the left cardiac ventricle of mice or golden hamsters, it penetrates well into the brain, but possibly both in the MB and the reduced leucoMB forms [21]. After this mode of administration, MB penetrates neurons differentially and is found both in the cytoplasm of a subset of neurons and in the extracellular matrix [21]. Furthermore, clinical studies show that serious transient neurological signs and symptoms develop in patients, who are given MB infusions after parathyroidectomy, if they are taking serotonin reuptake inhibitors or other antidepressants; this also strongly suggests that MB crosses the blood–brain barrier [22]. Passage of MB into the brain despite ionization may be facilitated by the dispersed charge distribution around the molecule, which may facilitate its passage through membranes [10]. Isobolic potential curves encompassing the MB molecule indicate that charges on the nitrogen and sulfur atoms are not localized and are almost equally distributed on the surface of the molecule (Fig. 1).

Other possible factors influencing membrane penetration of MB are differences in ionization and lipophilicity between MB and leucoMB, its reduced form. The pK_a of MB is about 0 to −1; hence, it is completely ionized in the pH range of 1–8 found in the gastrointestinal system [23]. Furthermore, the partition coefficient (log P) of MB was reported to be negative (−0.96); substances with a log P value below 0 are considered hydrophilic [10,23]. From the chemical point of view, given its hydrophilicity and its positive charge, MB would not be expected to pass lipid bilayer membranes [24]. However, cationic MB is reduced to the neutral leucoMB by redox systems in erythrocytes and peripheral tissues [12,15,16,23]. In isolated perfused rabbit lungs, approximately 16% of the MB entering the pulmonary artery was shown to be reduced before emerging from the pulmonary veins [25]. LeucoMB has a pK of 5.8, resulting in only 33% protonation, as opposed to MB with a pK value close to zero. Uncharged leucoMB is more than 20 times more lipophilic than MB [26]. Since lipophilic compounds easily pass the blood–brain barrier [24] and there are significant differences in the biological activities of MB and leucoMB, it is currently not clear, which form of MB mediates its biological actions.

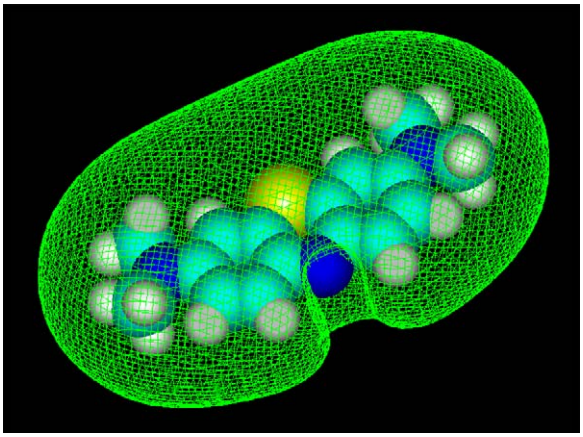

Fig. 1. The isopotential surface surrounding the methylene blue molecule was modeled in 3D space. Carbon, hydrogen, nitrogen, and sulfur atoms are represented by the colors cyan, white, blue and yellow, respectively. The green mesh represents the isopotential surface. The image was produced by Hyperchem version 6, using charges computed after minimizing the structure of MB by the semi-empirical method in the program.

MB has been shown to be taken up by cells, accumulate and dimerize in the cytoplasmic organelles, and to cause cell toxicity and DNA damage in various cell types [10,12,16]. At concentrations higher than 10 μM, MB forms dimers, with the dissociation constant being 170 μM [10,16], and causes cell toxicity. MB accumulation in various tissues is thus a complex process reflecting changes in MB reduction rates by the tissue, dye uptake, and the status of the tissue metabolic functions [10,12,16,25].

When administered i.v., MB demonstrates multi-compartmental pharmacokinetics with a terminal plasma half-life of 5–7 h [15]. Interestingly, i.v. administration of MB differs markedly with regard to organ distribution compared with oral administration. While oral MB results in higher intestinal and liver concentrations, i.v. administration results in higher MB concentrations in the brain [15].

Total urinary recovery of MB ranges from 53 to 97% of its oral dose [23]. The color of the urine following oral administration of MB was shown to be unrelated to the amount absorbed, since a considerable percentage of the dye (33–78%) recovered in the urine was excreted as stabilized leucoMB [15,23]. In clinical applications, MB usually produces blue-green urine, blue sclera and stained clothing. This benign discoloration can be alarming to patients, although it is self-limiting and disappears within a few days of discontinuing the drug.

From the toxicological point of view, MB is relatively nontoxic and has an enviable safety record [27,28]. In one notable pediatric case report [29], a child was given a dose that was 16 times the recommended maximum. The child's skin was intensely blue, but there were no other documented ill effects. Most side effects of MB appear to be dose-dependent and do not occur with doses <2 mg/kg, a dose range that is widely used in the clinical applications of MB. In *in vitro* studies, MB demonstrates biological actions at a wide range of concentrations, from 0.1 nM to 10 μM, and toxic effects have only been reported at concentrations higher than 100 μM. The oral LD_{50} of MB has been estimated to be 1180 mg/kg

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