

Review

Central & Peripheral Nervous Systems

Ademetionine (S-adenosylmethionine) neuropharmacology: implications for drug therapies in psychiatric and neurological disorders

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Ademetionine (S-adenosylmethionine; SAMe) is a ubiquitous metabolite present in all cells and biological fluids, and serves as a methyl donor in a multitude of different methylation reactions involving proteins, phospholipids, catecholamines and DNA. Pharmaceutical preparations of some stable salts of SAMe are available for parenteral and oral use in humans, and have been shown to increase plasma and cerebrospinal fluid SAMe concentrations. In experimental studies administration of SAMe is associated with increases in brain monoamine neurotransmitters and β -adrenergic and muscarinic receptor functions. These neuropharmacological effects are postulated to be involved in the antidepressant activity of SAMe which has been confirmed in numerous controlled studies. Preliminary studies indicate that SAMe has therapeutic potential in the treatment of other CNS disorders including dementia, acquired immune deficiency syndrome (AIDS)-associated myelopathy, and brain ischaemia. This review will focus on recent experimental and clinical aspects of SAMe in the central nervous system, and the therapeutic use in psychiatric and neurological disorders.

Keywords: *ademetionine, S-adenosylmethionine, brain ischaemia, dementia, depression, human immunodeficiency virus infection, methionine, methylation, monoamines, myelopathy*

Exp. Opin. Invest. Drugs (1997) 6(4):417-426

1. Introduction

Ademetionine (S-adenosylmethionine) is a naturally occurring compound present in all living cells, performing a vital role in many important and diverse cellular reactions. It acts as a methyl donor to acceptor molecules such as proteins, phospholipids, catecholamines, indolamines and DNA.

SAMe (**Figure 1**) is a highly labile compound and this contributed to the delay in considering it as a potential

pharmaceutical product. Early studies showed that SAMe is an effective antidepressant, a finding that has since been confirmed in numerous clinical trials [1-4]. In addition, the literature contains many controlled studies indicating that SAMe is effective in the management and treatment of chronic liver disease [5] and osteoarthritis [6]. Although SAMe may have various pharmacological actions related to diverse clinical uses, this paper will focus on the role of SAMe in the central nervous system (CNS) and its potential therapeutic use in psychiatric and neurological disorders.

2. Synthesis and metabolism of Ademetionine

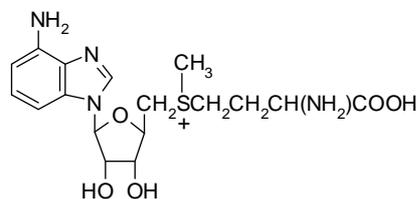
The enzymatic synthesis of SAME was first described in 1952, and involves the adenylation of methionine at the expense of ATP in a reaction catalysed by methionine adenosyltransferase (MAT) [7]. This enzyme is found widely distributed in all tissues and multiple forms have been described. Liver and other peripheral tissues may contain two or even three isoenzymes with K_m values for methionine ranging from 7 - 500 μM [8,9]. In contrast, only one form of MAT with a K_m for methionine of 5 μM is present in CNS tissue [10], a value that is close to the brain tissue methionine concentration. The kinetics of the MAT isoenzymes dictate that, after exogenous administration of methionine, there is a dose-dependent increase in SAME concentration in liver. However, because brain MAT is saturated at a methionine concentration less than the normal physiological concentration, there is no appreciable increase in SAME [11].

SAME serves an important biological function as the sole methyl donor in multitudinous cellular methylation reactions [12]. Most cells contain several SAME-dependent methyltransferases that can transfer the methyl group to the oxygen, nitrogen or sulfur atoms of both small and large molecules (**Figure 2**, reaction 2). For example, the syntheses of creatine from guanidinoacetate, sarcosine from glycine, phosphatidylcholine from phosphatidylethanolamine and adrenaline from noradrenaline, and the methylation of carboxyl residues of various proteins and cytosine residues of DNA all use SAME as the methyl donor. The product of all SAME-dependent methylation reactions is S-adenosylhomocysteine (SAH) (**Figure 2**). SAH is rapidly metabolised to homocysteine and adenosine by the enzyme SAH-hydrolase. Homocysteine is produced entirely as a product of methylation reactions as it is totally absent from any dietary source. It constitutes an important branch-point metabolite as it may undergo:

- remethylation to methionine by either vitamin B₁₂-dependent *N*5-methyltetrahydrofolate-homocysteine methyltransferase (or methionine synthetase) or by betaine-homocysteine methyltransferase (BHMT), thus completing a cycle which in essence conserves methionine
- irreversible condensation with serine to form cystathionine leading to cysteine and ultimately the formation of glutathione, a major cellular anti-oxidant.

BHMT is absent from the CNS tissue of various animal species [13] and from human brain tissue [14]. The CNS

Figure 1: Chemical structure of ademetionine.



de novo synthesis of methionine is, therefore, dependent on an adequate supply of vitamin B₁₂ and methyltetrahydrofolate to maintain normal methionine synthetase activity. Furthermore, the daily dietary intake of methionine is not sufficient to maintain the amount required for SAME synthesis. In animals [15] or humans [16,17] a deficiency in vitamin B₁₂ or methyltetrahydrofolate can lead to a reduction in or absent methionine synthetase activity resulting in depleted cellular methionine levels. This consequently leads to increased homocysteine levels, and decreased concentrations of methionine and SAME in brain or cerebrospinal fluid (CSF).

SAME may also be metabolised to decarboxylated SAME, which is involved in the synthesis of spermidine and spermine (**Figure 2**). In this process, the carbon atoms 2, 3, and 4 of the methionine moiety of SAME are incorporated into these polyamines, which are recognised as cell growth factors.

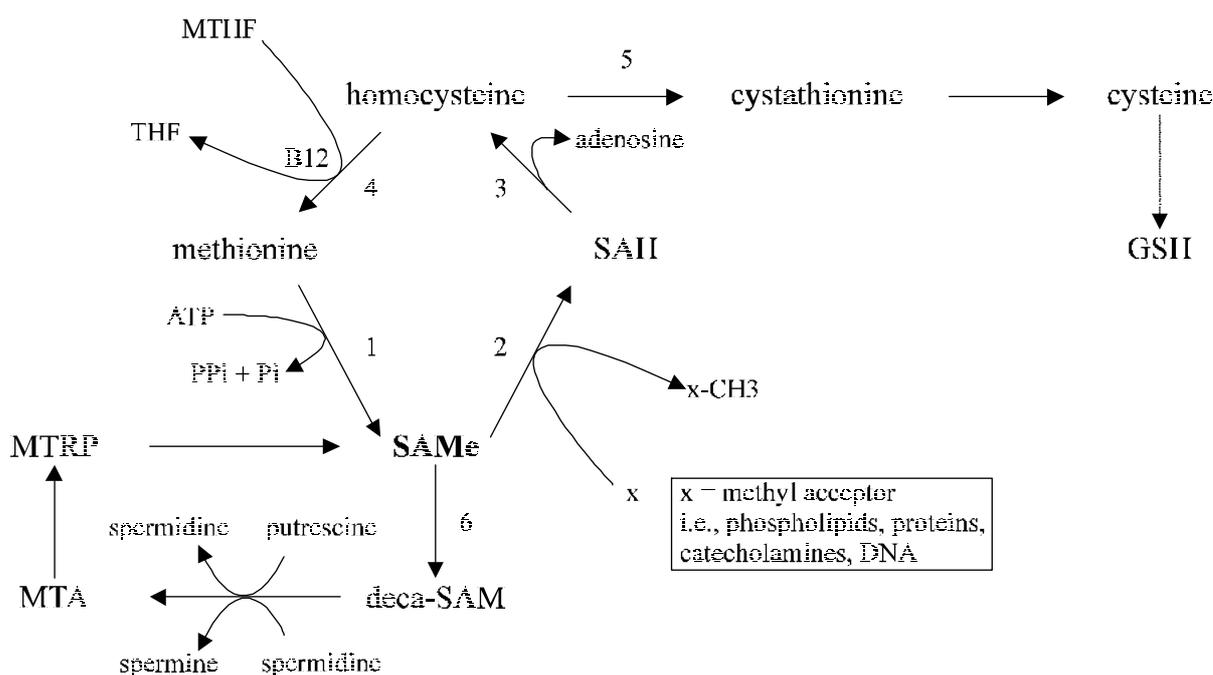
3. Pharmacokinetic properties of Ademetionine

The pharmacokinetics of SAME have been studied by measuring the decay of the drug in plasma after iv. administration of 100 mg (1.49 ± 0.08 mg/kg) and 500 mg (7.45 ± 0.4 mg/kg) (mean \pm SEM) to six healthy volunteers [18]. A biexponential decay was observed with a terminal disposition phase starting about 60 min after administration. The apparent volumes of distribution after the low and high doses were 407 ± 27 and 443 ± 36 ml/kg (mean \pm SEM), respectively. Total urinary excretion of the drug was 30 ± 3 and 34 ± 8 mg at 8 and 24 h after the administration of a 100 mg dose. At the same times after a 500 mg dose the excretion was 189 ± 11 and 201 ± 10 mg, respectively. Both drug elimination and renal excretion were almost complete within 24 h, and the ratio between renal and total clearances indicates that at both doses more than half of the SAME administered was metabolised. This suggests that body accumulation of SAME is unlikely at least up to the doses studied.

Figure 2: Metabolism of ademetionine (SAdMe). The key enzymes involved are:

1. Methionine adenosyltransferase; 2. X-methyltransferase; 3. Adenosylhomocysteine hydrolase; 4. Methionine synthetase; 5. Cystathionine synthetase; 6. SAdMe-decarboxylase.

ATP: Adenosine triphosphate; Deca-SAM: Decarboxylated-S-adenosylmethionine; GSH: Glutathione; MTA: Methylthioadenosine; MTHF: Methyltetrahydrofolate; MTRP: Methylthioribosephosphate; PPi: Pyrophosphate; SAH: S-adenosylhomocysteine; SAdMe: S-adenosylmethionine (Ademetionine); THF: Tetrahydrofolate.



Experimental studies have shown that SAdMe is able to cross the intestinal wall and increase plasma levels. Early studies in rats revealed that absorption of the drug is much better after intraduodenal administration compared to oral administration [19]. In a Phase I study the administration of enteric-coated tablets of SAdMe in varying doses of 400, 600 and 1000 mg to three male subjects increased plasma concentrations, in a dose-dependent manner, between 30 - 50 times basal values [20]. Despite substantial increases above physiological concentrations, the systemic bioavailability after oral SAdMe administration appears to be low. However, oral administration of [methyl- ^{14}C]-SAdMe (200 mg; 0.02 $\mu\text{Ci}/\mu\text{mol}$) to healthy volunteers showed that urinary excretion of radioactivity during the first 48 h was $15.5 \pm 1.5\%$, and faeces contained $23.5 \pm 3.5\%$ of the radioactivity up to 72 h [19]. These findings indicate that approximately 60% of the radioactivity is incorporated into stable pools. A comparison of the rapid

metabolism of SAdMe after an iv. or oral dose of [methyl- ^{14}C]-SAdMe (50 mg/0.4 mCi/mmol) has been performed in six male volunteers [19]. Plasma radioactivity rapidly decreased after iv. administration, corresponding to the decay of the unmodified product. In contrast, after oral administration plasma radioactivity increased with time, reaching a peak between 8 and 24 h after treatment. The higher radioactivity found after oral administration, compared to iv. administration at the later time intervals, suggests that SAdMe given orally is actively metabolised with the methyl group being incorporated into stable pools such as proteins and phospholipids. These observations are supported by a recent study showing that, after oral administration of a single 100 mg dose of double-labelled [methyl- ^3H : ^{35}S]-SAdMe, 62% of [^3H] and 43.7% of [^{35}S] radioactivity, remained in the body after five days [21]. Plasma concentrations of radioactivity were much

higher than those of the unmodified drug, suggesting a strong pre-systemic metabolism of absorbed SAME.

In relation to the neuro-pharmacological action of SAME, it is essential to demonstrate that the drug can penetrate the blood brain barrier (BBB). Several studies indicate that parenteral and oral administration of SAME can increase CSF concentrations. In dogs an iv. injection of 8 mg/kg of SAME followed by an iv. infusion of 12 mg/kg of SAME for 6 h was associated with a steady hourly increase in CSF SAME levels with a 20- to 40-fold increase over basal values after 6 h [19]. CSF SAME levels have also been studied in a placebo-controlled trial after the parenteral administration of 200 mg SAME daily for 14 days to depressed patients [22]. At 2 and 24 h after the last injection CSF SAME levels were significantly increased by 65% and 12%, respectively, compared to baseline values, indicating that the drug can cross the BBB. Similarly, administration of oral SAME (400 mg t.d.s for 4 - 8 months) to four patients with Alzheimer's dementia significantly increased both plasma and CSF SAME levels [22]. There is also evidence that the drug crosses the BBB intact. Due to the chiral nature at the sulfonium centre of the molecule, SAME can exist in both (*S,S*) or (*R,S*) form. Intravenous and oral pharmaceutical formulations of SAME contain approximately 20 - 30% of the (*R,S*)-SAME diastereomer, which is slowly metabolised enzymatically. In a recent study the parenteral administration of 800 mg SAME daily for 7 - 14 days to HIV-infected patients was associated with marked increases of both diastereomers in CSF [23]. The increase of the (*R,S*) form in CSF indicates that the drug can cross the BBB intact, the integrity of which, in the patients studied, were found to be preserved.

4. Neuropharmacology of Ademetionine

4.1 Monoamine neurotransmitters

The neuropharmacology of SAME has been the subject of three extensive reviews, in 1986 [24], 1987 [25] and 1994 [26]. Preclinical studies indicate that SAME has stimulatory effects on monoamine metabolism and/or turnover. Thus, SAME treatment has been reported to increase rat brain concentrations of noradrenaline [27,28], and serotonin (5-HT) [29,30]. In man, parenteral SAME administration is associated with a significant increase in CSF concentrations of the 5-HT metabolite, 5-hydroxyindole acetic acid [31], and the dopamine metabolite, homovanillic acid [32]. The stimulatory effect of SAME on central monoaminergic neurotransmitters has been postulated to be the mechanism of its antidepressant effect, although it does not share a mode of action that is typical of

standard tricyclic antidepressants. Recent *in vivo* microdialysis studies in the rat indicate that SAME increases dopaminergic tone. In one study chronic (200 mg/kg daily ip. for 7 days), but not acute, SAME inhibited the apomorphine-induced decrease in striatal dopamine [33]. Another study reported that chronic administration of SAME (200 mg/kg daily ip. for 7 days) increased striatal dopamine and the accumulation of L-DOPA after inhibition of aromatic amino acid decarboxylase (AADC) with NSD 1015 [34]. The accumulation of L-DOPA is indicative of an increase in tyrosine hydroxylase activity. *In vitro* studies support the *in vivo* findings as pre-incubation of striatal tissue with SAME was shown to have a stimulatory effect on tyrosine hydroxylase by reducing the K_m for the pterin substrate [35]. This effect was inhibited by SAH and the mechanism of activation by SAME was reported to be *via* increased protein carboxymethylation.

SAME has been studied in several animal models that are predictive of possible antidepressant activity [36]. SAME dose-dependently (12.5, 25, 50, 100 and 200 mg/kg sc.) decreased immobility time in the forced swimming test in mice and rats, an effect that was antagonised by haloperidol. The reduction of the immobility time evoked by antidepressants is regarded as a result of activation of the dopamine system. In addition, D-amphetamine induced locomotor hyperactivity in rats was significantly increased by chronic SAME (50 mg/kg sc. twice daily for 14 days). SAME dose-dependently (12.5, 25 and 50 mg/kg sc.) reduced hypothermia induced by apomorphine in mice, although it did not affect hypothermia induced by clonidine or reserpine. Apomorphine hypothermia is potentially antagonised by antidepressants (mainly tricyclics), as well as by amphetamine-like compounds and β -adrenergic agonists. The effect of SAME on apomorphine-induced hypothermia is consistent with its effect on inhibition of apomorphine-induced decreases in striatal dopamine, measured by *in vivo* microdialysis [35].

In contrast to these findings a recent study reported that rats given an intraventricular injection of SAME (doses ranging from 0.2 - 1.5 μ mol/rat) develop specific behavioural changes that resemble Parkinson's disease. These include tremors, rigidity, and hypokinesia accompanied by a 50.1% depletion in dopamine content in the caudate nucleus. These findings are in direct conflict with the reports described above on activation of the dopaminergic system after parenteral or sc. administration of SAME in rats [37]. It is relevant to note that the administration of 100 mg/kg sc. of SAME had no effect on behavioural function and exploratory activity in rats in an open field test [36].

4.2 Receptor systems

Chronic treatment with SAME is associated with an increase in density of β -receptors, and a decrease in the affinity of α_1 adrenoceptors for phenylephrine in rat cerebral membranes [38]. In 30 month old rats the binding of the β -adrenergic agonist [3 H]-dihydroalprenolol to rat brain membranes is decreased compared to young, 3 month old, rats. Chronic treatment of old rats with SAME was shown to reverse this effect and also decrease the membrane microviscosity [39]. Dopamine-sensitive adenylate cyclase activity, which was reduced in aged rats, was also restored to normal. These effects of SAME on β -adrenergic receptors are consistent with the earlier findings that an increase in erythrocyte phospholipid methylation increases β -adrenoreceptor-adenylate cyclase coupling [40].

The number of muscarinic receptors in the striatum and hippocampus of aged rats is significantly lower than the number in young animals. Treatment of aged rats with 50 mg/kg of SAME for 30 days restored the number of muscarinic receptors to levels found in the striatum and hippocampus of young animals [41]. In this study the *in vitro* addition of SAME to hippocampal membranes from aged rats resulted in a significant increase in the number of muscarinic binding sites, an effect antagonised by S-adenosylhomocysteine (SAH), a methyltransferase inhibitor. The reduction in muscarinic receptor density was postulated to be related to a decrease in neuronal membrane fluidity induced by ageing. SAME by virtue of its ability to act as a methyl donor may increase the fluidity of cell membranes by stimulating phospholipid methylation. Other investigators have shown that treatment with 10 mg/kg of SAME for 30 days significantly increased the number of M₁ muscarinic receptors in young rat forebrain. No changes were reported for the M₃ and M₄ muscarinic subtypes [42].

SAME enhances [3 H]-diazepam and [3 H]-GABA binding to crude synaptic plasma membranes from rat cerebellum. This was associated with increased [3 H]-methyl group incorporation into membrane phospholipids, and both the binding activities and phospholipid methylation could be inhibited by pre-treatment with SAH [43].

The effect of SAME on receptor systems is of particular interest as recent evidence suggests that age changes in the plasma environment, especially those resulting in increased viscosity, may be responsible for G protein-receptor coupling/uncoupling dysfunction [44]. The beneficial effects of SAME treatment suggest a possible strategy for various systems which exhibit G-protein receptor coupling/uncoupling dysfunction.

5 Neuropsychiatry of Ademetionine

5.1 Depression

Review articles on the efficacy of SAME in the treatment of depressive disorders have been published in 1988 [1], 1989 [2] and in 1994 [3]. The later and most comprehensive review performed a meta-analysis of clinical trials with SAME between 1973 and 1992. Overall, there were 13 uncontrolled trials enrolling 377 patients, 11 controlled trials with SAME *vs.* placebo enrolling 402 patients, and 14 controlled trials with SAME *vs.* tricyclic antidepressants enrolling 389 patients. The results of the meta-analysis showed a greater response rate with SAME than placebo, with a global effect size of 38% for partial to full responders (decrease in Hamilton score > 25%) and 17% for full responders (decrease in Hamilton score > 50%), with an average effect size of 27.5%. Meta-analysis of trials comparing SAME *vs.* other antidepressants gave a global response of 92% for SAME, and 85% for tricyclic antidepressants (global effect size of 7%) among partial to full responders, and a global response of 61% for SAME and 59% for tricyclic antidepressants (global effect size of 1%) among full responders. These results indicate that the efficacy of SAME in treating depressive disorders is superior to that of placebo and comparable to that of standard tricyclic antidepressants. Furthermore, relatively few side-effects were reported in the various trials after administration of SAME.

The efficacy of SAME in treating depressive disorders has been confirmed in several other studies since the meta-analysis report by Bressa [3]. In a multicentre open-label study, involving 195 outpatients, the administration of SAME (400 mg daily im.) was accompanied by a relatively fast symptomatic improvement [45]. In this study, mean Hamilton scores (HAM-D) were significantly reduced by 28.9% and 48.7% after 7 and 15 days of treatment, respectively, compared to the baseline value (mean \pm SD; 22.8 \pm 5.3). In another double-blind study, in which 40 patients received either 200 mg per day im. of SAME or placebo in addition to oral imipramine (IMI), the onset of clinical response occurred earlier in the SAME-IMI group than in those receiving the placebo-IMI combination [46]. The SAME-IMI combination is suggested to accelerate neurochemical changes associated with antidepressant effects, thereby shortening the therapeutic latency. It is relevant to note that both acute and chronic administration of imipramine significantly reduces rat brain SAME concentrations by 57% [47].

The antidepressant activity of SAME has recently been tested in two double-blind, multicentre, controlled studies, designated MC1 and MC2, in patients with

Table 1: HAM-D scores (17 items) pre- and post-treatment and percentage changes in patients with basal HAM-D \geq 26.

		N	Pre-treatment (mean \pm SD)	Post-treatment (mean \pm SD)	% Δ
MC1	Placebo	35	30.0 \pm 3.2	21.7 \pm 9.7	27.6
	SAMe	40	29.9 \pm 4.0	17.7 \pm 8.6 [§]	40.8
MC2	SAMe	57	29.6 \pm 2.9	18.8 \pm 8.2	36.5
	CIMI	65	29.3 \pm 3.5	15.0 \pm 6.8 ^{§§}	48.8

[§]p = 0.05 SAMe vs. placebo
^{§§}p = 0.01 CIMI vs. SAMe
 CIMI: Clomipramine; SAMe: S-Adenosylmethionine

major depression [48]. MC1 was a placebo-controlled trial where 800 mg of SAMe was administered iv. for 3 weeks. MC2 compared iv. SAMe for 3 weeks (800 mg/day) with iv. clomipramine (CIMI; 100 mg/day). The combined analysis of the results of the two studies in patients with basal HAM-D \geq 26 is presented in **Table 1**, and shows that SAMe has an intermediate antidepressant effect between iv. placebo and iv. CIMI. In the MC1 trial MADRS scores decreased from 34.7 ± 6.1 to 20.6 ± 12.2 in the SAMe group and from 34.8 ± 6.8 to 26.1 ± 12.6 in the placebo group ($p = 0.025$ SAMe vs. placebo). Similarly the scores of the psychopathological depressive core items of HAM-D (1, 2, 3, 7 and 8) improved from 11.6 ± 1.8 to 6.2 ± 4.2 with iv. SAMe and from 11.5 ± 1.8 to 8.4 ± 4.2 with iv. placebo ($p < 0.05$ SAMe versus placebo). In the MC2 trial the drug-related adverse events and drop-outs for adverse events were significantly lower ($p < 0.05$) in SAMe than in CIMI, showing a better tolerability profile of SAMe in comparison to CIMI.

5.3 Dementia

Several studies indicate that a CNS methyl group deficiency may play a role in the aetiology of Alzheimer's disease (AD). Reduced SAMe levels have been reported in CSF [22] and in several different brain regions [49] in patients with AD. One consequence of reduced brain SAMe levels may be a decrease in the conversion of phosphatidylethanolamine to phosphatidylcholine. In support of this, reduced phosphatidylcholine levels in AD post-mortem brain have been reported [50], and significant changes in brain phospholipid metabolism could be detected *in vivo* with phosphorous 31 magnetic resonance spectroscopy in the early stages of AD [51]. Furthermore, in four patients with AD the administration of SAMe 200 or 400 mg iv. for 14 days led to a significant increase in red cell membrane fluidity that was associated with an increase in phospholipid methylation [52]. In a preliminary study of AD, administration of oral SAMe for 3 -

5 months (400 mg, 3 times daily) increased plasma, and CSF SAMe concentrations [22], and improved measures of cognitive function as well as mood and speed of mental processing were noted [53,54]. In elderly patients with impaired cognitive and vigilance function treatment, a schedule of both parenteral and oral SAMe for 2 months was associated with a significant improvement in measures on the Mini-Mental State examination and the Sandoz Clinical Assessment Geriatric Scale [55]. The lack of adequate treatments for AD warrants an urgent need for further controlled studies testing the efficacy of SAMe on cognitive function.

5.4 Acquired immune deficiency syndrome-dementia complex and associated myelopathy

AIDS-dementia complex (ADC), which usually presents in the later stages of HIV-infection, is characterised by cognitive impairment which may be accompanied by motor and behavioural dysfunction. The neuropathology of ADC includes a vacuolar myelopathy that bears a striking histological resemblance to subacute combined degeneration of the cord (SACD), which accompanies vitamin B₁₂ and folate deficiency [56]. ADC is clinically evident in 30% of HIV-infected patients, with about half developing a myelopathy, although post-mortem examination of brains from patients with AIDS has revealed abnormalities in up to 88% of cases [57,58]. The similarity in the vacuolar myelopathy seen in patients infected with HIV and vitamin B₁₂ or folate deficiency is of particular interest as a disturbance in the SAMe methylation pathway have been reported in both. Reduced SAMe concentrations in CSF have been shown in three independent studies of HIV-infected patients, one in children [59] and two in adults [23,60]. The cause of the reduction in CSF SAMe concentrations in HIV-infection is not known. Reduced SAMe concentrations in CSF have been reported in patients with SACD due to vitamin B₁₂ or folate deficiency [17], and in demyeli-

nating children with inborn errors of the methyl-transfer pathway [16]. In the later study treatment with methyl donors (methyltetrahydrofolate, betaine, methionine and SAME) is associated with remyelination as assessed by magnetic resonance imaging (MRI).

Of particular interest is a recent study on the use of methionine in the treatment of AIDS-associated myelopathy [61]. Ten patients with progressive AIDS myelopathy and abnormal sensory-evoked potentials were treated with methionine, 3 g orally twice per day for 6 months. Post-treatment clinical evaluation showed that seven patients had a mild to moderate improvement of lower limb strength, sphincter control and erectile function. In four patients this was associated with an improvement in sensory-evoked potentials, and in memory scores. Based on previous experimental and clinical observations it is likely that methionine is acting by restoring brain SAME concentrations, and increasing methyltransferase activity. These studies imply that SAME may also be beneficial in the treatment of AIDS-associated myelopathy since administration of parenteral SAME has been shown to increase CSF SAME concentrations in HIV-infected patients. No side-effects were with this treatment reported [62]. If SAME proves to be an effective treatment for this disorder its use may be advantageous, as chronic high doses of methionine have been associated with hepatotoxicity, ascribed to the production of highly toxic mercaptans resulting from the limited capability of mammalian organs to metabolise methionine to SAME [62-64]. More detailed controlled studies on the efficacy of methionine and SAME are required to confirm these preliminary observations.

5.5 Brain ischaemia

There is extensive evidence suggesting that SAME protects against ischaemic brain damage in experimental models. For instance, SAME administered for a 2 week period prior to inducing brain ischaemia in gerbils, by bilateral ligation of the carotid arteries, corrected changes in polar lipids by reversing the decrease in phosphatidylcholine and choline plasmalogen [65]. Several independent studies have shown that the administration of SAME can improve cerebral energy metabolism in the post-ischaemic rat brain by increasing creatine phosphate, ATP and cAMP levels [66-68]. Glucose utilisation [69,70] was improved and cerebral blood flow was increased [69]. Moreover, SAME has been shown to protect hippocampal CA1 neurones from degeneration and necrosis [70], and accelerate recovery [66] in rats subjected to transient and brief forebrain ischaemia. SAME administration has also been shown to significantly improve working memory impairment induced by cerebral ischaemia in rats [71]. These experimental studies indicate that

clinical trials to examine the efficacy of SAME in stroke and cerebrovascular ischaemia are warranted.

6. Patent and drug development activities

SAME has been launched in several markets including Italy, Germany and Spain by the BASF subsidiary, Knoll Farmaceutici. Several patents on SAME stable salts have been granted to Knoll Farmaceutici. Among them SAME-1,4-butanedisulfonate (US5102791) has been chosen for pharmaceutical development because of its high stability and tolerability.

7. Expert opinion

SAME is an interesting compound because of the multitude of metabolic pathways in which it participates in every cell. The cellular uptake of SAME, and in particular its transport across the BBB, is a controversial issue. Nevertheless, unequivocal evidence has recently been presented to show that, after parenteral or oral administration, SAME is transported intact across the BBB, as determined by increased CSF concentrations of the two diastereomers. As this review has described, SAME has various neuropharmacological effects that increase CNS monoamine neurotransmitters and receptor function. The mechanism(s) of its neuropharmacological actions are not presently clear, and it is not known if they are mediated at the membrane level or after entry into target cells. It is likely that at least some of the effects of SAME are mediated through changes in phospholipid metabolism on the external surface of cellular membranes, as a number of studies outlined in this review have implied. There are two phospholipid-methyltransferases on the cell membrane surface that can be reached by exogenously administered SAME and may affect membrane fluidity, viscosity and, ultimately, receptor function.

It is clear that after more than 20 years of clinical investigation, numerous trials have confirmed that SAME has antidepressant activity. It is an atypical antidepressant in that its mode of action is unlike that of standard tricyclic antidepressants (TCA). As a drug it is very well-tolerated and devoid of side-effects or toxicity, except for the induction of mania that has been reported in a few patients with bipolar depression [72]. SAME should, therefore, be a good choice of antidepressant in elderly patients who cannot tolerate the anticholinergic effects of some of the more established antidepressants. This may also apply to depressed patients suffering from chronic cardiovascular disease, where standard antidepressants are contraindicated. A recent study in 48 patients with major

depression associated with internal illness (including cardiovascular disease, respiratory disorders, digestive disorders, endocrino-metabolic and various malignancies) showed that administration of SAME for 28 days resulted in a significant improvement in the mean score for the Beck's depression inventory [73]. Although minor side-effects were reported, none were serious enough to warrant withdrawal from the study. Furthermore, SAME may be an appropriate alternative choice in the treatment of depression in patients with malignancies, as experimental studies have shown that some standard antidepressant drugs (amitriptyline and fluoxetine) can suppress immune function, and stimulate malignant growth in rodents at clinically relevant doses [74].

8. Conclusions

The diverse neuropharmacological and clinical effects of SAME are in all probability related to the fact that SAME participates as a methyl donor in a multitude of cellular biochemical reactions. Methyl group deficiency has been implicated as a pathogenic mechanism in various neuropsychiatric illnesses including depression, dementia and some disorders in which demyelination occurs [75]. Therefore, there is a rational basis for the use of SAME as a CNS methyl group stimulant. Experimental and clinical studies indicate that SAME is a promising antidepressant and shows potential in drug treatment for other CNS disorders including cognitive dysfunction, AIDS-associated myelopathy and brain ischaemia. Research efforts should focus on determining the efficacy of SAME in dementia and AIDS-associated myelopathy where at present no suitable treatments are available.

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