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Review

Pharmacology of dimethyl sulfoxide in cardiac and CNS damage

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Abstract:
The pharmacological effects of dimethyl sulfoxide (DMSO) administration include some desirable properties that may be useful in the treatment of medical disorders resulting in tissue injury and compromised organ systems.These properties include the reported effects of DMSO on impaired blood flow, suppression of cytotoxicity from excess glutamate release that may result in lethal NMDA-AMPA activation, restriction of cytotoxic Na^+ and Ca^{2+} entry into damaged cells, blocking tissue factor (TF) from contributing to thrombosis, reduction of intracranial pressure, tissue edema, and inflammatory reactions, and inhibition of vascular smooth muscle cell migration and proliferation that can lead to atherosclerosis of the coronary, peripheral, and cerebral circulation. A review of the basic and clinical literature on the biological actions of DMSO in cardiac and central nervous system (CNS) damage or dysfunction indicates that this agent, alone or in combination with other synergistic molecules, has been reported to neutralize or attenuate pathological complications that harmed or can further harm these two organ systems. The effects of DMSO make it potentially useful in the treatment of medical disorders involving head and spinal cord injury, stroke, memory dysfunction, and ischemic heart disease.

Key words:
dimethyl sulfoxide, DMSO, heart disease, stents, stroke, traumatic brain injury, spinal cord trauma

Introduction

Dimethyl sulfoxide (DMSO) has a variety of biological actions that have made it the target of numerous pharmacological studies [67]. Over the past 40 years, more than 10,000 articles on the biological implications and 30,000 articles on the chemistry of DMSO have appeared in the scientific literature. In the United States, DMSO received approval from the FDA in 1978 for use in the treatment of intersticial cystitis by intravesicular administration [59]. This review will examine the basic and clinical studies that have been reported on the biological actions of DMSO in the area of CNS damage and ischemic cardiac disease as well as the reported neuroprotective role of DMSO in cerebral ischemia and trauma. Our brief review will attempt to provide some insight into the cellular and molecular targets of DMSO in an effort to better understand its clinical usefulness.

Heart disease

Systemic vascular resistance and hemodynamics were studied in a canine model of myocardial ischemia by

ligating the left anterior descending (LAD) coronary artery in order to abruptly drop cardiac output to simulate myocardial infarction [45]. Systemic vascular resistance was significantly reduced and cardiac output increased 3 h after a low dose DMSO bolus injection, however, higher cerebral blood flow (CBF) values were noted in the DMSO group compared to the control animals after only one hour (Fig. 1) [45]. There were no reported significant differences in heart rate, mean arterial pressure, pulmonary artery wedge pressure, or cerebral or pulmonary resistances in the DMSO--treated animals as compared to non-ligated controls [45]. This study did not speculate on why DMSO was able to restore cardiac output and CBF following LAD ligation, but improvement of cardiac output is considered an essential feature for treating a variety of cardiac disorders affecting both heart and brain [76].

These findings are of interest in light of more recent data on the protective activity of DMSO on tissue factor (TF) expression in human endothelial cells in response to TNF-α or thrombin exposure [8]. TF is generally accepted to be a key protein in the activation of coagulation and thrombus formation [47], and a cause of acute coronary syndromes and myocardial infarction [73].

TNF-α is elevated in acute coronary disease and is found at concentrations high enough to induce TF levels in coronary vessels [47]. Moreover, it was additionally reported that DMSO prevented proliferation and migration of vascular smooth muscle cells from the human aorta [8], an outcome that could have clinical application in treating coronary thrombosis and myocardial infarction (Fig. 1).

Previous studies had shown that DMSO is a powerful inhibitor of platelet aggregation [25, 64], a reaction that might involve the inhibition of prostaglandin platelet-aggregating arachidonic acid metabolites by DMSO [60]. No post-thrombotic consequences have been reported in humans or animals following high dose DMSO administration for platelet deaggregation [16, 25, 28].

Presently, clopidogrel bisulfate (Plavix) is one of the leading prescriptive anti-platelet agents used to reduce the risk of heart attacks and strokes in high risk patients. Post-marketing experience, however, has shown that although rare, thrombotic thrombocytopenic purpura is a serious side-effect of clopidogrel and should be used with caution [3].

Heart muscle homeostasis depends on the optimal flux of Na^+ and Ca^{2+} for its proper rhythmic contractions, and when an equilibrium of influx and efflux of these two ion species fails, it results in rhythm and contractile dysfunction. Drugs that prevent abnormal sodium influx into heart tissue provide effective protection against Na^+ and Ca^{2+} overload. Key players in regulating cardiac muscle homeostasis are ion channels and these are the prime targets for drugs preventing Na^+ and Ca^{2+} overload [10, 58] (Fig. 1).

Drugs that block abnormal Na^+ influx into heart tissue (class I agents) can prevent some cardiac arrhythmias by partially interfering with sodium channels that inhibit abnormal depolarizations [38].

It has been reported that DMSO has an effect on blocking Na^+ and Ca^{2+} entry into cells [8, 38]. Since substantial Na^+ and Ca^{2+} entry into myocytes typically occurs after cardiac arrhythmias and myocardial infarction, DMSO administration may prevent this inward cellular ion flux while preserving K^+ outflux from cardiac tissue. The mechanisms exerted by DMSO on Na^+ and Ca^{2+} channels need to be further investigated in mammalian models since the results of such studies could produce extremely useful and relatively safe agents for a variety of cardiac disorders affected by changes involving these cations.

Central nervous system (CNS) injuries

In the last 30 years, the most productive area of research and application in the use of DMSO has been in traumatic brain injury (TBI) and in stroke.

Table 1 summarizes the biological actions of DMSO against a variety of pathological events as reported in the literature. As seen in the Table, DMSO exerts neuroprotective effects on cellular and subcellular components associated with an assortement of tissue insults particularly involving brain and spinal cord trauma and stroke. These neuroprotective effects have been shown in animal models of CNS injury and in humans with traumatic brain injury and ischemic stroke.

DMSO was introduced as a potential therapeutic agent for head and spinal cord injury and for stroke in the early 1970s by de la Torre and his group [15–23] following a series of studies on non-human primates. These reports were confirmed by others using a variety of animal models involving CNS trauma [1, 2, 6, 9, 24, 37, 39, 51].

Tab. 1. Reported biologic activities for DMSO

Pathologic Event	DMSO
intracranial pressure increase (ICP)	reduces [20, 42, 44]
cerebral edema	reduces [9, 37, 53]
free radical formation	Scavenges [60, 63, 64]
cerebral ischemia	increases flow [16, 18, 41]
inflammation	suppresses [24, 34, 66]
calcium influx	attenuates [46]
Na^+ channel activation	blocks [46]
NMDA-AMPA channel activation	suppresses [46]
arterial thrombosis	suppresses [8]
glutamate excitotoxic death	antagonism [46]
tissue factor expression	suppresses [8]
vascular smooth muscle cells (VSMC)	prevents proliferation & migration [8]
neurologic disability	reduces [13, 16, 41]

ICP and cerebral edema reduction is reported in animal and human brain after TBI or stroke. This action may be due to the ability of DMSO to scavenge excess free radicals and prevent damage from Na^+ and Ca^{2+} influx into brain cells. Reduction of NMDA-AMPA channel activation will lower glutamate excitotoxicity, which is believed to intiate a biochemical cascade ending in a cell death pathway that involves ionic flux abnormalities and NMDA-AMPA activation. Suppression by DMSO of tissue factor expression, a key protein in the activation of thrombus formation, and prevention of VSMC migration and proliferation may attenuate arterial wall responses to injuries such as plaque rupture injury after stroke. These actions by DMSO suggest that this agent is a potent neuroprotector and may reduce neurologic damage following CNS injuries

DMSO in experimental traumatic brain injury (TBI)

A traumatic brain injury is usually the result of a sudden, violent blow to the head. The severity of the injury can range from minor, with few or no lasting consequences, to major, resulting in profound disability or death. The severity of TBI is dependent upon the area of the brain affected, the degree of injury, and the age and health status of the traumatized patient.

The exact biochemical reactions involved in the effects of DMSO in traumatic brain injury remain unclear. However, it has been reported that DMSO has some desirable properties that are considered to be useful in managing the brain trauma patient: i) it increases CBF without altering blood pressure [6, 9, 53], ii) it reduces intracranial pressure (ICP) quickly without a rebound effect and lowers tissue edema [24, 42, 44], iii) it is a potent diuretic that does not affect cardiac rate [6, 9, 42, 44], iv) it blocks Na^+ channel activation [32, 38, 64], v) it is a powerful free radical scavenger [63, 64, 70], vi) it prevents glutamate excitotoxic neuron death and suppresses NMDA-AMPA-induced ion currents and excessive Ca^{2+} influx into cells [46], vii) it suppresses tissue factor (TF) expression and reduces thrombus formation [8], and viii) it inhibits vascular smooth muscle cell (VSMC) proliferation and migration [8].

The molecular events involved in items i-viii are crucial in *cell-death pathways* that are generally associated with CNS damage, such as TBI and stroke. It should be noted that very small concentrations of DMSO may exert significant effects on *in vitro* cerebral metabolism, but its activity *in vivo* requires considerably higher concentrations to elicit a biological response.

For example, the use of $^1H/^{13}C$ NMR spectroscopy in a guinea pig cortical brain slice model revealed that extremely low concentrations of DMSO (0.000025%) can affect the metabolism of of [3-^{13}C]pyruvate, resulting in an increased net flux into the Krebs cycle, thus decreasing the net flux into the glycolytic end products lactate and alanine. Also, this produces a gradual shift in the lactate/pyruvate ratio in favor of pyruvate in the presence of higher DMSO concentrations [56]. Pyruvate has been shown to increase the mitochondrial proton gradient and increase the ATP level as a consequence [74]. We believe that the positive action of DMSO on an injured mammalian brain is related to the ability of this molecule to raise brain cell ATP levels that are generally suppressed or exhausted following prolonged ischemia, which is secondary to physical or physiological injury to the parenchyma [16, 18, 20].

Consequently, the ability of a therapy to increase CBF in managing TBI is critically important in light of the hypometabolism associated with such injuries and the rapid death of penumbral neurons that can occur from secondary damage. Secondary damage can develop over hours and days, and can involve excitatory neurotransmitter release, excess free-radical generation, gene activation, calcium/sodium-mediated cell damage, neuronal energy crisis, and inflammatory reactions (Fig 1).

Preventive neuronal salvage from such injuries therefore should aim to control the effect of secondary damage on penumbral neurons undergoing cerebral ischemia due to their proximity to the lesion site and their effect on impaired cerebral autoregulation and reduced cerebral perfusion pressure [57]. Further

damage or control of penumbral neurons can have a significant impact on the neurologic recovery of the traumatized patient [35, 42].

Treatment of brain edema after TBI presents a challenge for many clinicians. Several animal and human studies indicate that DMSO can quickly reduce edema and ICP following severe TBI [9, 24, 39, 42, 44, 53]. Whether the anti-edema property of DMSO can be explained by its potent diuretic action, its anti-inflammatory properties, or its ability to block excessive Na^+ and Ca^{2+} entry into cells that can induce cytotoxicity, requires further study [8, 16, 46].

DMSO and molecular activity

Drugs that block abnormal Na^+ influx into brain cells have been shown to exhibit strong neuroprotective activity in animal models of brain ischemia/hypoxia. Moreover, a number of clinical trials are now in progress to test the effects of this class of drugs on cerebral ischemia [7, 10, 58, 71].

DMSO has been shown to be a Na^+ channel blocker and it is partly this action that could explain its neuroprotective activity in brain cells following physical trauma and ischemic stroke [2, 17, 24, 42, 44] (Fig. 2). The Na^+ channel blocking activity could, in part, also contribute to its beneficial effect when administered to patients presenting with high ICP secondary to severe, closed head injuries [42, 44] or in the presence of cerebral bleeding resulting in clinically elevated ICP [53].

At clinical doses, DMSO has been shown to suppress, in a reversible manner, excessive calcium influx into cells and channel-opening of the ionotropic receptor channels N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA), which are known to be activated by glutamate during oxidative or metabolic stress [46]. This "excitotoxic" process by glutamate, which can damage or kill neurons, has been recently reported to be blocked by DMSO [46] (Fig. 1).

DMSO in clinical TBI

TBI in humans can significantly affect many cognitive, physical, and psychological skills and can involve important cellular and molecular changes within the brain cells. During the past two decades, understanding of the pathophysiology of TBI has increased dramatically, allowing for management of this injury [35] (Fig. 3).

The treatment of brain edema after TBI presents a challenge for many clinicians. Considerable animal and human studies indicate that DMSO can quickly lower edema and ICP following severe TBI [9, 22, 24, 39, 42, 44, 53]. Whether DMSO's anti-edema property can be explained by its potent diuretic action, its anti-inflammatory properties, and increase of cerebral perfusion or its blocking effect of excessive Na^+ and Ca^{2+} entry into cells that can induce cytotoxicity, requires further study [8, 16, 40, 46, 53].

Specific biological actions exerted by *iv* DMSO may help explain its positive effects when it is administered to patients presenting with high ICP secondary to severe, closed head injuries (Tab. 1). Clinical pilot studies in humans have reported the potential usefulness of intravenous (*iv*) DMSO following severe, closed head injury. Ten patients with severe head injuries were given *iv* DMSO in a 28% solution and responded very well to therapy, resulting in a reduction in their intracranial pressure (ICP) within 24 h following trauma. ICP elevation in these patients at the time of admission ranged from 40–130 mm Hg. After a 3 month follow-up, seven of the DMSO-treated patients showed mild to no deficits, two patients (20%) died of their injuries and one patient remained severely impaired [42]. Historically, mortality for this type of injury is estimated at 60–70% [57]. The results of this head injury study was confirmed in another trial on 10 patients given DMSO at a comparable dose following a severe head injury with essentially similar results [44]. In the second study, DMSO was given as an *iv* bolus and was shown to rapidly reduce increased ICP in nine patients while increasing the cerebral perfusion pressure (CPP) [44]. This outcome improved the neurological course and outcome of the eight survivors without affecting the systemic blood pressure or producing a rebound effect on ICP [44].

DMSO in experimental brain ischemia

The ability of DMSO to increase CBF in ischemic-hypoxic models has been investigated. Cerebral hy-

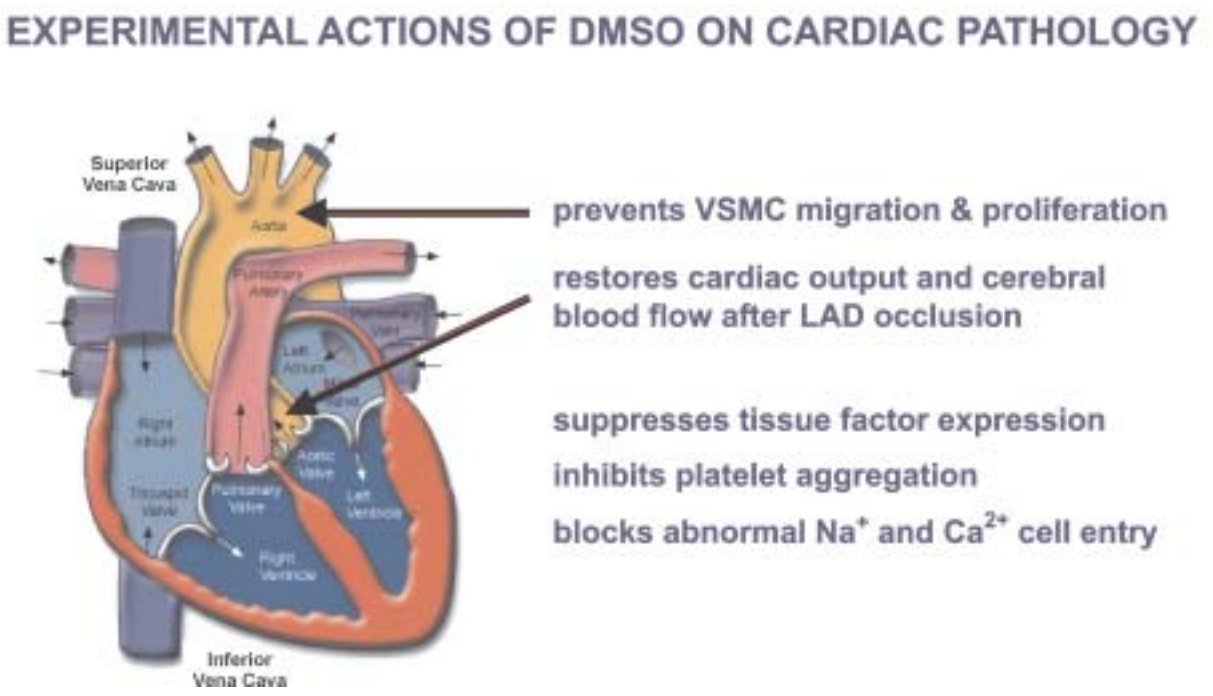

Fig. 1. Experimental findings on some of the effects of DMSO administration relevant to cardiac pathology. See text for details. VSMC – vascular smooth muscle cells; LAD – left descending coronary artery

poperfusion was induced in rats subjected to permanent, bilateral occlusion of the common carotid arteries, thus creating memory deficits, astrocyte proliferation, and cyclooxygenase-2-positive neuron loss in the dentate gyrus [27]. After DMSO treatment, rats recovered from their memory disability and showed a reduced loss of neurons in the dentate gyrus when compared to non-treated controls, suggesting that this agent confers significant protection in the experimental ischemia model [28].

In isolated dog brains subjected to complete ischemia, DMSO administration during reoxygenation resulted in a significant increase in ATP associated with markedly lower lactate levels and good recovery of EEG and auditory evoked potentials [31]. Thus, an increase in ATP combined with reduced energy consumption may reflect favorable changes in the balance of energy supply and demand during ischemic/hypoxic events such as in stroke.

The relevance of DMSO in stroke is supported by a study showing DMSO's neuroprotective ability against middle cerebral artery (MCA) occlusion in rats [2]. Reduced infarct volume was found after *iv* administration of DMSO (1.5 g/kg) 1–2 h after arterial occlusion and robust neuroprotection was observed when DMSO was given 20 h *prior* to occlusion, an outcome that suggests the potential usefulness of this agent in coronary artery bypass graft (CABG) surgery using drug-eluting stents [2]. The latter possibility has been applied following a study on mouse carotid artery photochemical injury using DMSO. It was found that DMSO prevented rapamycin and paclitaxel-induced upregulation of tissue factor expression. Rapamycin and paclitaxel are two popular agents used in drug-eluting stents for the treatment of acute coronary syndromes (see also Heart Disease above). Both rapamycin and paclitaxel are effective in reducing restenosis after percutaneous coronary intervention, but they are also associated with tissue factor expression, a possible cause of induced thrombosis in drug-eluting stents, which is their most important side-effect [72]. Also, this study demonstrated that DMSO inhibited vascular smooth muscle cell (VSMC) proliferation and migration [8]. VSMC migration and proliferation are essential elements in the hyperplasia lesion that occurs in cerebral, coronary, or peripheral atherosclerosis. Interventions with agents such as DMSO that prohibit or slow down this process can effectively control or reverse this pathologic process.

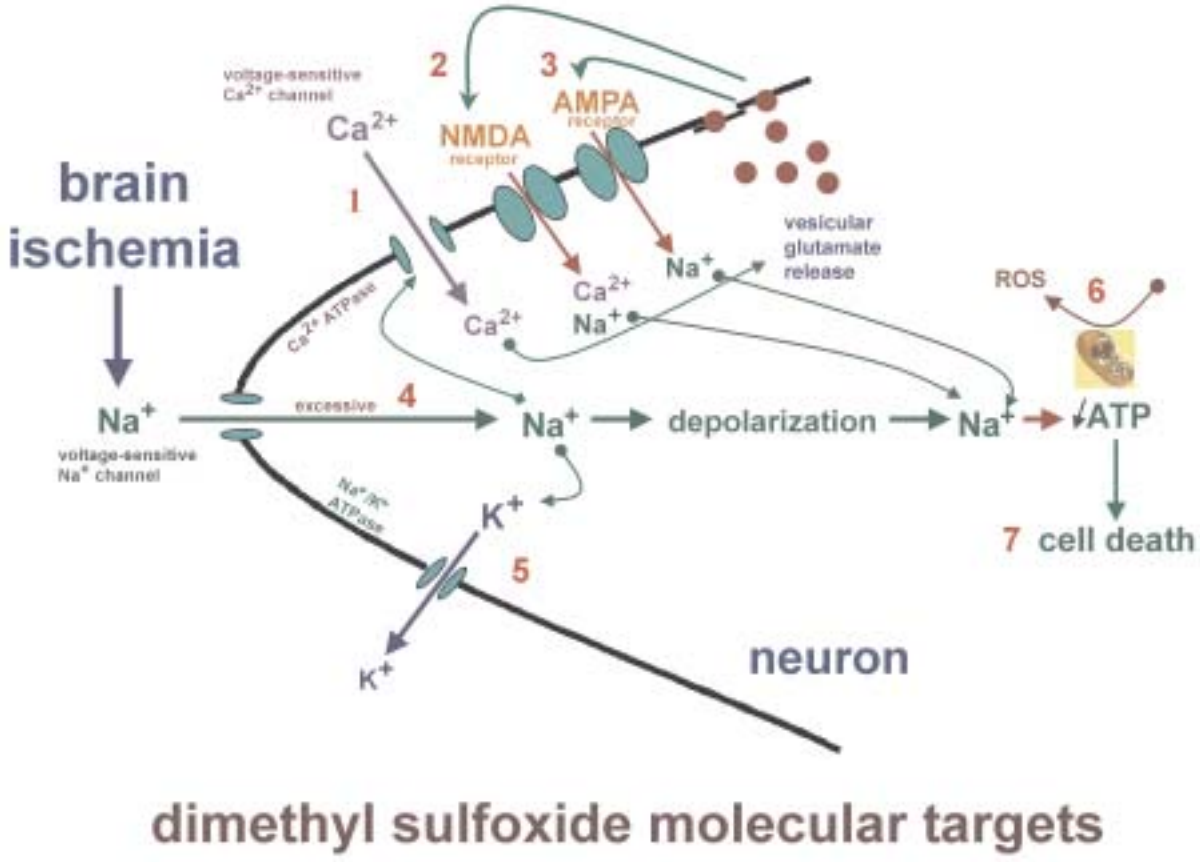

Fig. 2. Theoretical basis of presumptive neuroprotective qualities of DMSO and its possible molecular targets at the subcellular level based on experimental research findings (see text). DMSO is reported to suppress excessive calcium (Ca^{2+}) influx into cells (**1**) and blocks NMDA (*N*-methyl-D-aspartate) and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate) receptor channels (**2**, **3**) following ischemic events that can promote excitotoxic death of neurons. DMSO is reported to block sodium (Na^+) channel activation (**4**), a reaction seen after CNS injury that may activate a biochemical cascade resulting in intracytoplasmic potassium efflux (**5**), cell energy hypometabolism (↓ATP), reactive oxygen species (ROS) and free radical production (**6**), and cell death (**7**). DMSO has been shown to inhibit tissue factor expression, thrombus formation and vascular smooth muscle cell (VSMC) proliferation and migration (not shown), and elements known to contribute to ischemic vessel occlusion in organs

- **Detect structural damage (CT scan)**
- **Provide oxygenation/ventilation [when needed]**
- **Reduce ICP**
- **Restore CBF**
- **Maintain normal blood pressure**
- **Identify associated injuries**
- **Prevent secondary brain damage**

Fig. 3. Basic clinical approach to the head injured patient

The findings on the effects of DMSO on local and global ischemic processes have been supported by other reports. MCA occlusion that produces a large infarction volume was significantly reduced in rats treated with 1.0 ml of DMSO given 30 min after MCA [69]. In another study, ischemia was induced in the Mongolian gerbil by a 5 min period of bilateral common carotid artery occlusion followed by reperfusion for 5 days. The extent of CA1 pyramidal neuron loss was significantly reduced in gerbils treated with 2.8 mmol/kg DMSO *ip* [61].

DMSO treatment resulted in a protective effect in rats with MCA occlusion as evidenced by reduced lesion sizes measured with MRI at selected time points [55].

Nuclear factor κB (NF-κB) is a transcription factor involved in inflammatory responses. In a rat model of

hemorrhagic shock, 6 mg/kg DMSO was given in blood and resulted in end-organ modulation of NF-κB and heat shock protein expression, thus neutralizing the stress of hemorrhagic shock in rats. This modulation of hemorrhagic shock may result from inhibition of the NF-κB-dependent production of pro-inflammatory mediators [4].

Not all reports agree that DMSO is useful as an anti-edema agent. One study recently reported that DMSO (1%) used as a vehicle for drug administration may open the blood-brain barrier and increase fluid in the extracellular space possibly providing an avenue for development of vasogenic edema [43]. The mechanism underlying this reported action, however, remains unclear.

DMSO in spinal cord injury

DMSO has been used in experimental spinal cord injury, but it has not been studied in a large human population [33]. Results from animal experiments indicate that if a severe spinal cord trauma is treated with intravenous DMSO within 2 h, paralysis may be prevented [15, 40]. Most reports are consistent with this action by DMSO [29, 30, 34]. Treatment may consist of 1–2 g/kg in a 28–40% solution of DMSO diluted with either physiologic saline or 5% dextrose with water.

A comparison of DMSO with other standard therapies, such as steroids, hyperbaric oxygen, mannitol or urea, suggests that DMSO is far superior in experimentally-induced spinal injury. DMSO reportedly shows faster sensory-motor recovery, reduced neural damage to the cord, lower swelling of tissue after trauma, increased muscle tone return, and earlier return of somatosensory evoked potentials than comparable treatments [12, 15, 29, 30, 34, 78].

Other studies have shown that DMSO can protect axons and their myelin sheaths after spinal cord trauma while reducing inflammation, tissue cavitation, and increasing spinal cord blood flow [29, 30, 36, 66]. It was recently reported that DMSO is capable of rendering significant improvement in guinea pig axonal membrane following injury [68].

DMSO has shown synergistic activity when combined with fructose 1,6-diphosphate (FDP). FDP is an intermediate of anaerobic glycolytic metabolism and has been shown to restore the activity of the Embden-Meyerhof pathway and oxidative phosphorylation when administered during prolonged hypoperfusion states [48]. FDP can also inhibit oxygen-free radicals, stimulate anaerobic glycolysis, and increase production of ATP [49], the main energy fuel for cells and neurons [26]. The combination of DMSO + FDP to treat experimental brain trauma induced in mice, was reasoned to prevent or restore the loss of ATP in ischemic brain cells while simultaneously reducing progressive cerebral edema caused by the injury [20]. Consequently, it was anticipated that FDP would act primarily to protect ischemic brain tissue from energy substrate depletion, a common outcome after TBI, while DMSO would act to stabilize cell membranes from excess free radical formation and abnormal Ca^{2+} entry into cells while improving CBF by reducing intracranial pressure [19]. Although modest neuroprotection was seen after DMSO treatment alone, histopathological morphometry indicated that cortical and hippocampal CA1 neurons were markedly protected from damage when mice were treated with a combination of DMSO and FDP [20]. The findings indicated that combining FDP with DMSO resulted in considerable synergy in protecting mice from sensory-motor loss and neuronal brain damage and in ultimate survival stemming from a moderate or severe closed head injury [20]. DMSO has also been combined with the powerful platelet deaggregator and vasodilator prostacyclin (PGI_2) in experimental cerebral ischemia where the two agents resulted in significant cytoprotection of cortical catecholaminergic fibers and generated a sustained CBF increase of 68% over control values [19].

DMSO in memory dysfunction

In another study where DMSO and FDP were combined, rats were subjected to bilateral carotid artery occlusion or sham occlusion and tested 12 weeks later for visuo-spatial memory function [16]. After 14 weeks, bilateral carotid artery occluded rats showed severe visuo-spatial memory impairment at which time they were given DMSO + FDP *ip* for seven days and retested for visuo-spatial memory using a water maze. After administration of DMSO + FDP, a 54% improvement in memory was observed when compared to non-treated occluded rats [16]. The results of this

study indicated that a DMSO + FDP combination improved visuo-spatial memory secondary to chronic brain hypoperfusion, an outcome that may have relevant implications in the treatment of Alzheimer's disease [13, 14, 21, 62].

DMSO in human stroke

The previously described experimental studies led to a preliminary trial using DMSO + FDP in human stroke [41]. Eleven, mostly elderly, patients (average age 65), who presented with an ischemic stroke up to 12 h in duration were given *iv* infusions of 28% DMSO + FDP twice daily for an average of 12 days, while five control patients (average age 63) were given standard therapy [41]. Safety and tolerability were evaluated by clinical adverse effects to drug therapy. Efficacy of DMSO + FDP was assessed by MRI lesion size, magnetic resonance angiography of ischemic territory, and a 5-point neurologic recovery scale that rated sensory-motor function and level of consciousness. The results of this mini-trial suggested that DMSO + FDP administration appeared well-tolerated and resulted in improved or markedly improved neurologic status at 1, 3, and 6 months after treatment in 7 of 11 (63%) patients [41]. In contrast, 1 of 5 (20%) standard-treated patients showed 'improved' status only at the 3-month follow-up [41]. This preliminary trial indicated that DMSO + FDP is well tolerated by this group of elderly patients and could be of benefit in reducing neurologic disability after ischemic stroke. However, the mechanisms by which DMSO + FDP reduced the adverse neurological deficits of stroke, remain to be determined.

Toxicity

One of the most important questions about any medicinal therapy is safety. Adverse reactions to DMSO are relatively mild and can occur in relation to its concentration and its mode of administration. The best-documented side effect of DMSO treatment is intravascular hemolysis after intravenous infusion of 40% solution or greater which can result in urinary excretion of hemoglobin [75]. Despite a dose-dependent transient hemolysis with concommitant hemoglobinuria, no alteration in renal function occured [54]. The hemolysis appears to be related to osmotic changes caused by DMSO in erythrocytes. Intravascular hemolysis after *iv* can be prevented by using less than a 30% DMSO solution [41, 42, 44]. However, hypernatremia and fluid overload has been reported when DMSO is given at highly diluted rates of infusion, but 10% or less in severe head trauma patients [50]. This side effect can be avoided if 25–35% DMSO solution is given by *iv* [41, 42, 44, 53].

Autologous and allogeneic stem cell transplants are an established therapy for hematological and solid tumor malignancies. A cryopreservative is obligatory for autologous stem cell transplants and 10% DMSO is a standard carrier for stem cell transplants. Acute neurologic abnormalities associated with a transient, profound encephalopathy and cardiac and gastrointestinal effects immediately following infusion of stem cells suspended in the cryopreservative DMSO have been reported in some patients, suggesting an acute DMSO-induced systemic toxicity [11]. This toxic reaction, if not caused by other contributing factors [11], appears to be a rare occurrence. Other trials using infusion of DMSO-cryopreserved peripheral blood stem cells are reported to be safe even in patients with pre-existing cerebral disease [52].

An annoying, but non-serious side effect of DMSO administration by any route, is garlic-like breath due to the pulmonary excretion of its breakdown product dimethyl sulfide [67]. This odor can potentially interfere with double-blinded clinical trials when intravenous DMSO is used because the sulfide odor will easily identify the patient receiving this treatment. However, the odor problem caused by DMSO administration in clinical trials of this compound can be neutralized with scouting equipment that absorbs the dimethyl sulfide and maintains the room-air fresh.

Conclusions

The physiologic and pharmacologic properties and effects of DMSO are not completely understood. Nevertheless, several pharmacological effects exerted by DMSO are desirable for combating a variety of tissue insults and molecular abnormalities affecting the

heart and the brain. These properties include improvement of blood flow; suppression of cytotoxicity caused by excess glutamate release; restriction of toxic Na^+ and Ca^{2+} entry into cells; blockade of thrombosis caused by tissue factors; reduction of intracranial pressure, tissue edema, and inflammatory molecules; and prevention of vascular smooth muscle cell migration and proliferation that can lead to atherosclerosis of the coronary, peripheral, and cerebral circulation. Taken as a whole, DMSO, alone or in combination with synergistic molecules, may help neutralize pathological products harmful to the heart and brain in medical disorders involving head and spinal cord injury, stroke, memory dysfunction, and ischemic heart disease. It has not escaped our attention that other disorders that involve similar pathological events (Tab. 1) may also benefit from DMSO therapy. A perusal of the DMSO mammalian toxicity data from the literature indicates that this molecule is considered to be relatively safe and that reported adverse effects are rare when DMSO is administered in clinically established concentrations [5, 77].

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