Pharmacology of DMSO

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A wide range of primary pharmacological actions of dimethyl sulfoxide (DMSO) has been documented in laboratory studies: membrane penetration, membrane transport, effects on connective tissue, anti-inflammation, nerve blockade (analgesia), bacteriostasis, diuresis, enhancement or reduction of the effectiveness of other drugs, cholinesterase inhibition, nonspecific enhancement of resistance to infection, vasodilation, muscle relaxation, antagonism to platelet aggregation, and influence on serum cholesterol in experimental hypercholesterolemia. This substance induces differentiation and function of leukemic and other malignant cells. DMSO also has prophylactic radioprotective properties and cryoprotective actions. It protects against ischemic injury.

The pharmacologic actions of dimethyl sulfoxide (DMSO) have stimulated much research. The purpose of this report is to summarize current concepts in this area.

When the theoretical basis of DMSO action is described, we can list literally dozens of primary pharmacologic actions. This relatively brief summary will touch on only a few: (A) membrane penetration: (B) membrane transport; (C) effects on connective tissue; (D) anti-inflammation; (E) nerve blockade (analgesia); (F) bacteriostasis; (G) diuresis; (H) enhancement or reduction of effectiveness of other drugs; (I) cholinesterase inhibition; (J) nonspecific enhancement of resistance to infection; (K) vasodilation; (L) muscle relaxation; (M) enhancement of cell differentiation and function; (N) antagonism to platelet aggregation; (O) influence on serum cholesterol in experimental hypercholesterolemia; (P) radioprotective and cryoprotective actions; (Q) protection against ischemic injury; and (R) free radical scavenging.

Primary Pharmacological Actions

A. Membrane Penetration

DMSO readily crosses most tissue membranes of lower animals and man.

Employing [35_s]DMSO, Kolb et al. (66) evaluated the absorption and the distribution of DMSO in lower animals and man. Ten minutes after cutaneous application in the rat, radioactivity was measured in the blood. In man radioactivity appeared in the blood 5 min after cutaneous application. One hour after application of DMSO to the skin, radioactivity could be detected in bones.

Denko (28) and his associates applied 35_s-labeled DMSO to the skin of rats. Within 2 hr a wide range of radioactivity was distributed in all organs studied. The highest values occurred in decreasing order in the following soft tissues: spleen, stomach, lung, vitreous humor, thymus, brain, kidney, sclera, colon, heart, skeletal muscle, skin, liver, aorta, adrenal, lens of eye, cartilage.

Rammler and Zaffaroni (95) have reviewed the chemical properties of DMSO and suggested that the rapid movement of this molecule through the skin, a protein barrier, depends on a reversible configurational change of the protein occurring when DMSO substitutes for water.

B. Membrane Transport

Nonionized molecules of low molecular weight are transported through the skin with DMSO. Substances of high molecular weight such as insulin do not pass through the skin to any significant extent. Studies in our laboratory have revealed that a 90% concentration of DMSO is optimal for the passage of morphine sulfate dissolved in DMSO (91). It would have been expected that 100% would provide better transport than 90% and the reason for an optimal effect at 90% DMSO remains unexplained. It is of course well known that 70% alcohol has a higher phenol:water partition coefficient than 100 % alcohol.

Spruance studied DMSO as a vehicle for topical antiviral agents, concluding that the penetration of acyclovir (ACV) through guinea pig skin in vitro was markedly greater with DMSO than when polyethylene glycol (PEG) was the vehicle. When 5% ACV in DMSO was compared with 5% ACV in PEG in the treatment of experimental herpes infection in the guinea pig, ACV/DMSO was more effective (119).

The possibility of altering the blood-brain diffusion barrier with DMSO needs additional exploration. Brink and Stein (12) employed [14_c]pemoline dissolved in DMSO and injected intraperitoneal into rats. It was found in larger amounts in the brain than was a similar dose given in 0.3% tragacanth suspension. The authors postulated that DMSO resulted in a partial breakdown of the blood-brain diffusion barrier in vitro.

There is conflicting evidence as to whether dimethyl sulfoxide can reversibly open the blood-brain barrier and augment brain uptake of water-soluble compounds, including anticancer agents. To investigate this, ^{123}I-human serum albumin, horseradish peroxidase, or the anticancer drug melphalan was administered iv to rats or mice, either alone or in combination with DMSO. DMSO administration did not significantly increase the brain uptake of any of the compounds as compared to control uptakes. These results do not support prior reports that DMSO increases the permeability of water-soluble agents across the blood-brain barrier (48).

Maibach and Feldmann (77) studied the percutaneous penetration of hydrocortisone and testosterone in DMSO. The authors concluded that there was a threefold increase in dermal penetration by these steroids when they were dissolved in DMSO.

Sulzberger and his co-workers (123) evaluated the penetration of DMSO into human skin employing methylene blue, iodine, and iron dyes as visual tracers. Biopsies showed that the stratum corneum was completely stained with each tracer applied to the skin surface in DMSO. There was little or no staining below this layer. The authors concluded that DMSO carried substances rapidly and deeply into the horny layer and suggested the usefulness of DMSO as a vehicle for therapeutic agents in inflammatory dermatoses and superficial skin infections such as pyodermas.

Perlman and Wolfe (90) demonstrated that allergens of low molecular weight such as penicillin G potassium, mixed in 90% DMSO, were readily carried through intact human skin. Allergens having molecular weights of 3000 or more dissolved in DMSO did not penetrate human skin in these studies. On the other hand, Smith and Hegre (117) had previously recorded that antibodies to bovine serum albumin developed when a mixture of DMSO and bovine serum albumin was applied to the skin of rabbits.

Turco and Canada (128) have studied the influence of DMSO on lowering electrical skin resistance in man. In combination with 9% sodium chloride in distilled water, 40% DMSO decreased resistance by 100%. It was postulated that DMSO in combination with electrolytes reduced the electrical resistance of the skin by facilitating the absorption of these electrolytes while it was itself being absorbed.

DMSO in some instances will carry substances such as hydrocortisone or hexachlorophene into the deeper layers of the stratum corneum, producing a reservoir (120). This reservoir remains for 16 days and resists depletion by washing of the skin surface with soap, water, or alcohol (121).

C. Effect on Collagen

Mayer and associates (79) compared the effects of DMSO, DMSO with cortisone acetate, cortisone acetate alone, and saline solutions on the incidence of adhesions following vigorous serosal abrasions of the terminal ileum of Wistar rats. Their technique had developed adhesions in 100% of control animals in 35 days. The treatments were administered daily as postoperative intraperitoneal injections for 35 days. The incidence of adhesions in different groups was DMSO alone, 20%, DMSO-cortisone, 80%; cortisone alone, 100%; saline solution, 100%.

It has been observed in serial biopsy specimens taken from the skin of patients with scleroderma that there is a dissolution of collagen, the elastic fibers remaining intact (109). Gries et al, (49) studied rabbit skin before and after 24 hours in vitro exposure to 100% DMSO. After immersion in DMSO the

Among the intriguing possibilities for the use of DMSO is its ability to alter bacterial resistance. Pottz and associates (78) presented evidence that the tubercle bacillus, resistant to 2000 lg of streptomycin or isoniazid, became sensitive to 10 lg of either drug after pretreatment with 0.5-5% DMSO.

Kamiya et al. (60) found that 5% DMSO restored and increased the sensitivity of antibiotic-resistant strains of bacteria. In particular, the sensitivity of all four strains of Pseudomonas to colistin was restored when the medium contained 5% DMSO. The authors recorded that antibiotics not effective against certain bacteria, such as penicillin to E. coli showed growth-inhibitory effects when the medium contained DMSO.

Ghajar and Harmon (41) studied the influence of DMSO on the permeability of Staphylococcus aureaus, demonstrating that DMSO increased the oxygen uptake but reduced the rate of glycine transport. They could not define the exact mechanism by which DMSO produced its bacteriostatic effect.

Gillchriest and Nelson (43) have suggested that bacteriostasis from DMSO occurs due to loss of RNA conformational structure required for protein synthesis.

G. Diuresis

Formanek and Suckert (38) studied the diuretic effects of DMSO administered topically to rats five times daily in a dosage of 0.5 ml of 90% DMSO per animal. The urine volume was increased 10-fold, and with the increase in urine volume, there was an increase in sodium and potassium excretion.

H. Enhancement or Reduction of Concomitant Drug Action

Rosen and associates (100) employed aqueous DMSO to alter the LD_{50} in rats and mice when oral quaternary ammonium salts were used as test compounds. In rats, the toxicity of pentolinium tartrate and hexamethonium bitartrate was increased by DMSO, while the toxicity of hexamethonium iodide was decreased.

Male (78) has shown that DMSO concentrations of upward to 10% lead to a decided increase in the effectiveness of griseofulvin.

Melville and co-workers (80) have studied the potentiating action of DMSO on cardioactive glycosides in cats, including the fact that DMSO potentiates the action of digitoxin. This effect, however, does not appear to involve any change in the rate of uptake (influx) or the rate of loss (efflux) of glycosides in the heart.

I. Cholinesterase Inhibition

Sams et al. (105) studied the effects of DMSO on skeletal, smooth, and cardiac muscle, employing concentrations of 0.6-6%. DMSO strikingly depressed the response of the diaphragm to both direct (muscle) and indirect (nerve) electrical stimulation, and caused spontaneous skeletal muscle fasciculations. DMSO increased the response of the smooth muscle of the stomach to both muscle and nerve stimulations. The vagal threshold was lowered 50% by 6% DMSO. Cholinesterase inhibition could reasonably explain fasciculations of skeletal muscle, increased tone of smooth muscle, and lower vagal threshold observed in these experiments. In vitro assays show that 0.8-8% DMSO inhibits bovine erythrocyte cholinesterase 16-18%.

J: Nonspecific Enhancement of Resistance

In a study of antigen-antibody reactions. Raettig (96) showed that DMSO did not diminish the immune response. In fact, the oral administration of DMSO to mice for 10 days prior to an infection with murine typhus produced a leukocytosis and an enhanced resistance to the bacterial infection.

K. Vasodilation

Adamson and his co-workers (1) applied DMSO to a 3-to-1 pedicle flap raised on the back of rats. The anticipated slough was decreased by 70%. The authors suggested that the primary action of DMSO on pedicle flap circulation was to provoke a histamine-like response. Roth (103) has also evaluated the effects of DMSO on pedicle flap blood flow and survival, concluding that DMSO does indeed increase pedicle flap survival, but postulating that this increase takes place by some mechanism other than augmentation of perfusion. Kligman (63-64) had

reduce or increase the vessel lumen obstruction, or chemical, i.e., reduce or increase the vessel lumen diameter (vasoconstriction/vasodilation).

Platelets, for example, can induce both conditions. Obstruction of the vessel lumen can result from platelet adhesion (platelet buildup in damaged vessel lining) or platelet aggregation. Platelet damage moreover can cause vasoconstriction or vasospasm by liberating vasoactive substances locally within the blood vessel or perivascularly, if penetrating damage to the vessel has occurred. There are two storage sites within platelets that contain most of these vasoactive substances. The alpha grapules contains fibrinogen, while the dense bodies store ATP, ADP, serotonin, and calcium, which can be secreted by the platelet into the circulation by a canalicular system (6). Thromboxane A_2 has also been shown to be manufactured in the microsomal fraction of animal and human platelets (86). All these vasoactive substances (with the exception of ATP) can cause significant reduction of blood flow by physical or chemical reactivity on the vasculature.

DMSO can antagonize a number of these vasoactive substances released by the platelets, which could consequently induce vasoconstriction, vasospasm, or obstruction of vessel lumen. For example, a study has shown that DMSO can inhibit ADP and thrombin-induce platelet aggregation in vitro (111). It may presumably do this by increasing the levels of cAMP (a strong platelet deaggregator) through inhibition of its degradative enzyme, phosphodiesterase (84, 101). DMSO is reported to deaggregate platelets in vivo following experimental cerebral ischemia (32, 55). This effect may be fundamental in view of the finding that cerebral ischemia produces transient platelet abnormalities that may promote microvascular aggregation formation and extend the area of ischemic injury (31).

The biochemical picture is further complicated by the possible activity of DMSO on other vasoactive substances secreted by the platelets during injury or ischemia. For example, the release of calcium from cells or platelets and its effect on arteriolar-wall muscle spasm may be antagonized by circulating DMSO (17, 104). Collagen-induced platelet release may also be blocked by DMSO (49, 110).

The following effects of DMSO are likely to be involved in its ability to protect against ischemic injury.

DMSO and PGTX Systems

Little is known about the actions of DMSO on the prostanoids (PG/TX). Studies have reported that DMSO can increase the synthesis of PGE, a moderate vasodilator (68). PGE can reduce platelet aggregation by increasing cAMP levels and also inhibit the calcium-induced release of noradrenalin in nerve terminals, an effect that may antagonize vasoconstriction and reduction of cerebral blood flow(59).

DMSO , it will be recalled, also has a direct effect on cAMP. It increases cAMP presumably by inhibiting phosphodiesterase (131), although an indirect action on PGI_2-induced elevation of platelet cAMP by DMSO should not be ruled out. Any process that increases platelet cAMP will exert strong platelet deaggregation.

It has also been reported that DMSO can block PFG_{2a} receptors and reduce PFE_2 synthesis (98). Both these compounds can cause moderate platelet aggregation and PFG_{2a} is known to induce vasoconstriction (67). The effects of DMSO on thromboxane synthesis are unknown. It could, however, inhibit TXA_2 biosynthesis in much the same way as hydralazine or dipyridamole (47) since it shares a number of similar properties with these agents: specifically, their increase of cAMP levels.

DMSO and Cell Membrane Protection

The ability of DMSO to protect cell membrane integrity in various injury models is well documented (44,73, 107, 130).

Cell membrane preservation by DMSO might help explain its ability to improve cerebral and spinal cord blood flow after injury (24). DMSO could be preventing impairment of cerebrovascular endothelial surfaces where PGI_2 is elaborated and where platelets can accumulate following injury. The effects by DMSO may be twofold: reduction of platelet adhesion by collagen (49, 110), and

DMSO inhibited histamine release induced by compound 48/80 at concentrations ongoing from 0.6 to 10%. At higher concentrations in the range of 20 to 40% the substance caused histamine release by itself. (15)

Experimental lens induced uveitis was produced in Lewis rats. Treatment of these animals by the intraperitoneal injection of DMSO resulted in a reduction of retinal vasculitis, hemorrhage, and necrosis.(97)

Morton and Moore (83) reported that lupus nephritis and death in mice were reduced when 3% water solutions of DMSO or $DMSO_2$ were given. The mechanism remains unclear but free-radical scavenging particularly with DMSO should be high on the list.

In the rat, DMSO protects against tissue injury and improves the course of endotoxemia. The severe small intestinal hemorrhage typical of E. shock was virtually abolished by DMSO.(11)

The authors (2) described an experimental study of craniocerebral trauma during ethanol intoxication. This experimental design simulated the situation where an individual imbibes 2 - 4 alcoholic drinks over a 1 hour period, then drives a motor vehicle and suffers a head injury. Albin and Bunegin postulated that intermediate metabolites of ethanol provides a large source of hydroxyl-free radicals in the presence of neuronal tissue damage and that these free radicals are effectively scavenged by DMSO. It is estimated that more than half of the fatal vehicular accidents in the U.S. involve individuals who have been drinking.

DMSO reduced post injury ankle stiffness in a rabbit hind limb model. The ankle stiffness after injury was reduced by 41%. The authors postulated free radical scavenging as a mechanism of action.(82)

Levett and associates evaluated the effects of DMSO on systemic and cerebral hemodynamic variables in the ischemic canine myocardium. The DMSO dosage used was 500 mg/kg as an i.v. bolus in 50% solution. The authors (72) concluded that DMSO exerted a protective effect on ischemic myocardium and was associated with a significant increase in cerebral blood flow.

Kennedy and Slymons (62) reported that DMSO suppressed radiation induced transformation <u>in vitro</u> even when DMSO treatments began as late as 10 days post irradiation. The authors presented evidence to suggest that free radicals may be important in the induction of malignant transformation <u>in vitro</u>.

Chemoprevention of experimental carcinoma in rats was studied by McCAbe et al. The author (75) used 5% DMSO, and 1% and 4% $DMSO_2$ in the drinking water concluding that DMSO and $DMSO_2$ were effective in the chemoprevention of DMBA induced mammary cancers. Other possible uses of DMSO and its major metabolites in cancer therapy are;

1. Chemopreventatives
2. Differentiating agents
3. Carrier for chemotherapeutic drugs
4. Non specific adjuvants

A reasonable hypothesis would be that agents which induce cancer cells to become more benign might effect oncogenes or oncogenic expression in some way.

Coles et al (19) evaluated DMSO as a free radical scavenger in protection of the spinal cord during ischemia. The authors employed dogs. The thoracic aorta was occluded and DMSO in a dosage of 0.1 gm/kg was injected into the occluded aortic segment. Animals were observed for evidence of paresis in the post operative period. Microscopic analysis revealed evidence of ischemic myelopathy in the control group but none in the treated group.

Smoke inhalation is the major cause of death in burn victims. Brown and his associates studied experimental burns with smoke inhalation in Ewes. Animals were given DMSO plus heparin per tracheostomy. All seven animals in the control group died. The seven sheep receiving DMSO plus heparin survived. The authors postulated that the free scavenger abilities of DMSO permitted recovery.(14)

DMSO was given in 1 and 2% concentration orally to mice. The authors reported a decrease in the amount of Anti DNA antibodies in the animals given DMSO. These data are in accordance with other studies demonstrating inhibition of autoantibodies by DMSO.(133)

DMSO blocks the precipitation of Bence-Jones protein. The authors treated two myeloma patients demonstrating that DMSO actually was associated with an increased removal of B-J protein.(81)

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