Available online at www.sciencedirect.com
SCIENCE DIRECT®
Biochemical Pharmacology 65 (2003) 1035–1041
Commentary
Biochemical Pharmacology
www.elsevier.com/locate/biochempharm

Multidisciplinary utilization of dimethyl sulfoxide:pharmacological, cellular, and molecular aspects

Nuno C. Santos*, J. Figueira-Coelho, J. Martins-Silva, Carlota Saldanha

Instituto de Bioquímica/Instituto de Medicina Molecular, Faculdade de Medicina de Lisboa, Av. Prof. Egas Moniz, P-1649-028 Lisboa, Portugal

Abstract

DMSO is an amphipathic molecule with a highly polar domain and two apolar methyl groups, making it soluble in both aqueous and organic media. It is one of the most common solvents for the *in vivo* administration of several water-insoluble substances. Despite being frequently used as a solvent in biological studies and as a vehicle for drug therapy, the side-effects of DMSO (undesirable for these purposes) are apparent from its utilization in the laboratory (both *in vivo* and *in vitro*) and in clinical settings. DMSO is a hydrogen-bound disrupter, cell-differentiating agent, hydroxyl radical scavenger, intercellular electrical uncoupler, intracellular low-density lipoprotein-derived cholesterol mobilizing agent, cryoprotectant, solubilizing agent used in sample preparation for electron microscopy, antidote to the extravasation of vesicant anticancer agents, and topical analgesic. Additionally, it is used in the treatment of brain edema, amyloidosis, interstitial cystitis, and schizophrenia. Several systemic side-effects from the use of DMSO have been reported, namely nausea, vomiting, diarrhea, hemolysis, rashes, renal failure, hypertension, bradycardia, heart block, pulmonary edema, cardiac arrest, and bronchospasm. Looking at the multitude of effects of DMSO brought to light by these studies, it is easily understood how many researchers working with DMSO (or studying one of its specific effects) might not be fully aware of the experiences of other groups who are working with it but in a different context.

Keywords: Dimethyl sulfoxide; Amyloidosis; Inflammation; Cell cycle; Cell differentiation; Cryopreservation

1. Introduction

DMSO [$(CH_3)_2SO$] is an amphipathic molecule with a highly polar domain and two apolar groups, making it soluble in both aqueous and organic media. Due to these physico-chemical properties, DMSO is a very efficient solvent for water-insoluble compounds and is a hydrogen-bound disrupter (see Ref. [1], for example). Despite being known since the nineteenth century (mainly due to its use in the wood industry), its biologic properties were only discovered in the 1960s. Since then it has been used for diverse laboratory and clinical purposes. DMSO is frequently used as a solvent in biological studies and as a vehicle for drug therapy. However, its side-effects (undesirable for these studies) are often neglected. In this article, we will try to present a global insight over the molecular, cellular, pharmacological, and toxicological effects of DMSO.

2. Pharmacological applications of DMSO

DMSO has been used in several human therapeutic situations. In 1978 it received approval by the United States Food and Drug Administration (FDA) for use in the treatment of interstitial cystitis, by intravesical instillation [2]. Its effects do not seem to be related to a detectable histamine release from mast cells [3]. It has been used successfully in the treatment of dermatological [4–6], urinary [7], pulmonary [8], rheumatic and renal [9] manifestations of amyloidosis. Basically through its anti-inflammatory and reactive oxygen species scavenger actions, its use has been purposed in several gastrointestinal diseases [10–14]. DMSO crosses the blood–brain barrier [15] and has been effective in the treatment of traumatic brain edema [16]. It has been also used in the treatment of musculoskeletal disorders [17], pulmonary adenocarcinoma [18], rheumatologic diseases [19,20], chronic prostatitis [21], dermatologic diseases [22–24], schizophrenia [25], and as a topical analgesic [26]. In addition, it has been suggested for the treatment of Alzheimer's disease [27]. Some of the reported effects of

* Corresponding author. Tel.: +351-21-7985136; fax: +351-21-7939791.
E-mail address: nsantos@fm.ul.pt (N.C. Santos).

0006-2952/03/$ – see front matter © 2003 Elsevier Science Inc. All rights reserved.
doi:10.1016/S0006-2952(03)00002-9

Table 1
Brief summary of the reported effects of DMSO in the treatment of different human and experimental animal model diseases

Disease	Actions/effects	Reference(s)
Interstitial cystitis	Improves treatment, but the effect is not related with mast cell release of histamine	[2,3]
Amyloidosis	Helps to control pruritus in macular and lichen amyloidosis, avoiding the recurrent deposition of amyloid in areas of trauma of the epidermis	[4]
	Causes regression of hyaline deposits in lipoid proteinosis	[5]
	Improves primary amyloidosis of the bladder (instillation)	[7]
	Reduces pulmonary infiltration and improves arterial blood gas levels in pulmonary amyloidosis associated with multiple myeloma	[8]
	Is effective in the treatment of some cases of primary amyloidosis when combined with cytoreductive chemotherapy	[28]
	Induces a decrease of the inflammatory activity of rheumatoid arthritis and an improvement of renal function, following 3–6 months of therapy, in patients with secondary amyloidosis	[9]
	Induces growth and blackish turn of scalp hair and beard	[6]
Gastrointestinal disorders	Has an anti-inflammatory effect in ulcerative colitis	[10]
	Associated with H_2 receptor blockers, is more effective for healing acute duodenal ulceration and prevention of its recurrence than H_2 receptor blockers alone	[11]
	Improves survival in patients bearing colon carcinoma	[12]
	Has a beneficial therapeutic effect in the mechanism of abdominal pain caused by alcohol-induced chronic pancreatitis	[13]
	Gives protection in stress-induced acute gastric mucosal injury	[14]
Brain edema	Has a beneficial effect in the treatment of traumatic brain edema	[16]
Rheumatologic disorders	Has a beneficial effect in the treatment of rheumatoid arthritis, reducing the associated pain	[19]
	Enhances the effect of glucocorticoids in the treatment of rheumatoid synovitis	[20]
Chronic prostatitis	Induces a positive result in the treatment of human chronic prostatitis	[21]
Schizophrenia	Has an antipsychotic action	[25]
Pulmonary adenocarcinoma	Improves the antiproliferative effect of interferon-α on human lung adenocarcinoma cells through an unknown mechanism	[18]
Dermatologic disorders	Has a beneficial effect in the topical treatment of herpes zoster	[22]
	Enhances the efficacy of fungicides in the treatment of dermatologic mycosis	[23]
	Is an effective and safe antidote that may be used with local cooling after the extravasation of certain drugs used in chemotherapy given intravenously, preventing the necrosis of tissues and ulceration	[24]
Experimental animal model	Inhibits collagen α1 gene expression, increase in tissue collagen content, hepatic stellate cell activation, synthesis of tissue inhibitors of metalloproteinase-2 and, consequently, the development of liver cirrhosis in mice	[29]
	Prevents the development of liver cirrhosis induced by thioacetamide	[29]

DMSO in the treatment of different diseases are summarized in Table 1.

Besides all of the previously referred to pharmacological applications in the treatment of different pathologies, several systemic side-effects from the use of DMSO have been reported, namely nausea, vomiting [30], diarrhea [31], severe hemolysis mimicking a hemolytic transfusion reaction [32], anaphylactic reactions manifested by rashes, flushing, and (occasionally) bronchospasm [33,34], renal failure [35], diastolic and systolic hypertension [36], bradycardia, heart block [37–39], and (rarely) pulmonary edema or cardiac arrest [40,41]. A significant side-effect of DMSO is a garlic-like breath odor and taste in the mouth due to the pulmonary excretion of a small percentage of DMSO as dimethyl sulfide [42]. Its topical application, although well tolerated, can cause mild transient local burning [24], skin rash, and pruritus [22]. A case of sulfhemoglobinemia after dermal application of DMSO in the treatment of interstitial cystitis has been reported, with fatigue, cyanosis, and dyspnea with mild exertion [4]. Serum hyperosmolality in the control of increased intracranial pressure with DMSO given intravenously has also been described [43]. This expected effect was also observed in human blood *in vitro* studies [44]. However, DMSO penetrates the cell membrane and causes an increase in osmolality both inside and outside the cell, preventing any significant hemolysis due to the formation of an osmotic gradient [45].

3. Cellular and molecular effects of DMSO

Zhang and Eyzaguirre [46] reported that the rise in intracellular calcium concentration induced by hypoxia in mouse glomous cells is blunted by the presence of DMSO. The studies of Choi *et al.* [47] with human promyelocytic leukemia HL-60 cells also indicated that the neurotensin-induced rise in intracellular [Ca^{2+}]

disappeared after treatment with DMSO. Michel [48] showed that in DMSO-treated human erythroleukemia cells, calcium elevations by adrenaline and neuropeptide Y were reduced significantly. Finally, Reynaud *et al.* [49] reported a similar DMSO interference with the hepoxilin A_3 effect on human neutrophils. These four recent findings are in accord with our observation that DMSO prevents the ionophore-induced calcium loading of human erythrocytes [44]. This coherence between results obtained with different biological systems and different modulators of the rise in intracellular [Ca^{2+}] suggests a nonspecific action of DMSO, disabling the expected effect of the modulator.

In the same study [44], we showed that there is an increase in the extracellular concentrations of K^+, Na^+, and Ca^{2+} in whole blood aliquots incubated with DMSO (2%, v/v). These findings are probably due to a DMSO-induced leakage of ions from human platelets, an effect that does not alter the plasma pH significantly [50]. At the molecular level, an explanation for the effect of DMSO on intracellular and extracellular ion concentrations is prevented by the divergence in the published studies of the

Table 2
Brief summary of the reported effects of DMSO in the study of the inflammation process, observed in experimental models

Actions/effects	Reference(s)
Inhibits interleukin-8 production in a dose-dependent manner, directly at the transcriptional level. Prevents adhesion of neutrophils to endothelium. Scavenges ClO^- and possibly reduces NADPH-oxidase activity	[57]
Inhibits human platelet aggregation induced by ADP, arachidonic acid (AA), platelet activating factor (PAF), and collagen, in a concentration-dependent manner, being a more effective inhibitor for aggregation induced by ADP and collagen than PAF or AA	[58]
Stimulates prostaglandin E_2 and 12-HETE (hydroxyeicosatetraenoic acid) production by bovine seminal vesicle prostaglandin synthase, and inhibits the production of tri-HETE produced via the lipoxygenase pathway	[58]
Induces a decrease in proteoglycan synthesis in a time-dependent manner, dehydration of the cartilage and chondrocyte death. Equine joints show a decrease in synovial leukocyte counts, reduced inflammatory response, and suppress matrix metabolism	[59,60]
Inhibits sepsis-induced activation of nuclear factor-κB (NF-κB), resulting in the suppression of intercellular adhesion molecule 1 (ICAM-1) gene expression in the livers of peritonitis septic rats	[61]
Enhances human cytomegalovirus replication by up-regulating the major immediate early promoter, in part, related to enhanced NF-κB and cyclic AMP response element binding protein activity	[62]
Potentiates tumor necrosis factor-α (TNF-α)-induced cytotoxicity in various human myeloid cell lines	[56]
Decreases the level of NF-κB activation in a macrophage-like cell line, correlated with decreased expression of cytokine messenger RNA and TNF-α bioactivity, suggesting that modulation of NF-κB activation may provide a mechanism through which antioxidants protect against endotoxemia in murine models	[63]
Enhances the production of several platelet-specific proteins, platelet factor 4, and platelet-activation-dependent granule external membrane protein	[64]
Inhibits formyl-methionyl-leucyl-phenylalanine (fMLP) and leukotriene B_4-induced leukocyte adherence in a dose-related manner in rat colon venular endothelium	[65]

Table 3
Brief summary of the reported effects of cell cycle, differentiation, and apoptosis studies, observed in experimental models

Type of study	Actions/effects	Reference(s)
Cell cycle	Inhibits c-*myc* expression, in different cell types	[66–68]
	Inhibits c-*myc* expression during the G_1 to S transition in adherent fibroblast cells arrested at $G_{0/1}$ by serum starvation	[69]
	Arrests the cell cycle of several human and mouse lymphoid cell lines at the G_1 phase	[70]
	Arrests the cell cycle of a transformed human B-cell line at G_1 phase and suppresses interleukin-6-induced differentiation into IgM-producing cells at a concentration lower than that affecting cell proliferation, suggesting that cell proliferation and differentiation are independent of each other	[71]
Differentiation	Down-regulates c-*myc* protein in the $G_{1/0}$ specific phase prior to the appearance of differentiation-associated markers	[72]
	May induce differentiation of malignant cells present in the marrow or alternatively in the body when it is infused back with the transplanted marrow	[73]
	Enhances the differentiation of leukemic cells to mature myelocytes	[74]
	Prevents dedifferentiation of normal cells. Cultured adult rat hepatocytes can be maintained and made to secrete albumin for more than 40 days	[75]
	Leads to the cessation of the proliferation of murine erythroleukemia cells and the production of a number of erythrocyte markers, such as hemoglobin	[76]
Apoptosis	Leads to the collapse of mitochondrial membrane potential, release of cytochrome *c* from the mitochondria, and activation of caspase-9 and -3, but not of caspase-8 (caspase cascade of mitochondrial apoptotic pathway is indispensable for DMSO-induced apoptosis). Induces apoptotic changes in a murine lymphoma cell line (concentration- and time-dependent effect) and down-regulation of Bcl-2	[77]
	Prevents apoptosis in lymphoma cells	[78]

effects of this solvent on transmembrane ion transport mechanisms. A DMSO-induced reduction of Ca^{2+} efflux was described for dorsal root ganglion cells from neonatal rats [51] and for skeletal muscle, cardiac muscle, and cerebellar vesicles [52]. At variance, the studies of Ogura *et al*. [53] with guinea pig ventricular myocytes indicated that incubation with DMSO had little effect on Ca^{2+} and inward-rectifier K^+ currents, moderately inhibited Cl^- and Na^+ currents, partially inhibited the Na^+ pump current, and markedly depressed the delayed-rectifier K^+ current. The data found in the literature for ATPase activities is again controversial. Different authors have reported an activation of purified erythrocyte membrane (Ca^{2+} + Mg^{2+})-ATPase by DMSO [54,55]. Using human erythrocyte ghosts and the same range of DMSO concentrations, McConnell *et al*. [56] showed that DMSO inhibits calmodulin-stimulated (Ca^{2+} + Mg^{2+})-ATPase and (Na^+ + K^+)-ATPase, without any significant effect on calmodulin-independent (Ca^{2+} + Mg^{2+})-ATPase and on Mg^{2+}-ATPase activities.

These and other reported cellular and molecular effects of DMSO (such as different effects related to inflammation, lipid metabolism, apoptosis, cell cycle, protein expression, differentiation, molecule binding, enzyme activity, reactive oxygen species scavenging, cell polarization, cryopreservation, and other experimental procedures) are summarized in Tables 2–5.

Table 4
Brief summary of the reported effects of DMSO in lipid metabolism and other studies, observed in experimental models

Type of study	Actions/effects	Reference
Lipid metabolism	Activates acid sphingomyelinase and accelerates the intracellular mobilization of low density lipoprotein (LDL)-derived cholesterol	[79]
	Increases the transfer of unesterified cholesterol between membranes	[80]
	Prevents the expected rise in serum cholesterol by 50%, but does not prevent cholesterol accumulation in aortic tissues, when administered in the drinking water of cholesterol-fed cockerels	[81]
	Reverse the abnormal processing of LDL cholesterol in mutant Niemann-Pick disease fibroblasts, namely the excessive lysosomal accumulation of LDL cholesterol and the delayed induction of cellular homeostatic responses associated with the uptake of LDL by the mutant cells. Accelerates the intracellular mobilization of LDL-derived cholesterol through effects that may reflect enhanced membrane permeability or cholesterol solubilization. Ameliorates a secondary deficiency of sphingomyelinase activity that can be present in these fibroblasts as a manifestation induced by excessive LDL cholesterol that accumulates in the lysosomes of the cells	[82]
	Reduces the accumulation of cholesterol in vascular and extravascular tissues, and partially prevents the development of dietary cholesterol-induced atherosclerosis (despite the severe hypercholesterolemia accompanying the cholesterol feeding), when administered in the drinking water of rabbits	[83]
	Reduces the binding, internalization, and degradation of exogenous LDL in human skin cultured fibroblasts; not acting by increasing the secretion of cholesterol by the cell	[83]
Other	Suppresses the expression of CD20	[71]
	Enhances the expression of sialyl $Lewis^x$ and sialyl dimeric $Lewis^x$ antigens on the surface of human gastric carcinoma cells, and the binding of *Limulus polyphemus* agglutinin (which specifically binds to cell-surface sialic acid)	[84]
	Modifies the protein conformation of mutant p53 to one recognized by a wild-type specific monoclonal antibody in a murine erythroleukemia cell line, accompanied by a translocation of the p53 protein from the cytoplasm to the nucleus	[85]
	Increases the synthesis of band 3 protein without noticeable changes in the synthesis of other membrane proteins erythropoietin-induced erythroid cells	[86]
	Enhances and maintains thyroid function for more than 13 days, with evidence of *de novo* synthesis and release of thyroid hormones, when added to the usual culture medium to preserve human thyrocytes extracted from patients with Graves disease	[87]
	Decreases glycosaminoglycan chain length in human erythroleukemia cell proteoglycans	[64]
	Decreases human erythrocyte aggregation indexes and leads to higher plasma concentrations of K^+, Na^+, and Ca^{2+}	[44]
	Protects against 1-methyl-4-phenylpyridinium (MPP^+) toxicity through the inhibition of OH radical-mediated oxidative injury in the substantia nigra	[88]
	Has positive and/or negative inotropic effects on perfused heart and isolated cardiac tissue preparations. Depresses nerve conduction velocity and affects enzymatic activity related to Na^+ pumping, second messenger production, and mitochondrial oxidative phosphorylation	[53]
	Is a free radical scavenger, protein kinase C activator, and myocardial contracture relaxant	[53]
	Blocks γ-aminobutyric acid-induced Cl^- current in rat dorsal root ganglion neurons	[53]
	Causes a small hyperpolarization and a prolongation of the action potential of guinea pig papillary muscles	[53]
	Has inotropic and chronotropic effects, affects various ATPase, and protects the heart against ischemic injury	[89]
	Inhibits the binding of prostaglandin $F_{2\alpha}$ to corporal luteal cell membranes	[83]
	Alters the permeability and stability of lysosomal membranes *in vitro*	[82]
	Induces an increase of intracellular [Ca^{2+}], dependent upon extracellular [Ca^{2+}], in dispersed bovine cells and cells isolated from human parathyroid adenomas	[90]

Table 5
Brief summary of the reported effects of DMSO in some of its technical applications

Application	Actions/effects	Reference
Cryopreservation	On the cryopreservation of human platelets, induces K^+, Ca^{2+}, and lactate dehydrogenase release from the intracellular space to the extracellular space, and strongly activates complement	[50]
	At moderate concentrations, preserves the structure of the seminiferous epithelium of rat testicular biopsies	[91]
	At 1.5 M, allows the cryopreservation of human islets with superior survival and preservation of post-culture function, when compared with 2.0 M or different ethylene glycol concentrations	[92]
	Together with a controlled rate of freezing, largely prevents the cellular damage in freezing, caused by the formation of ice crystal within the cells	[93]
	A final concentration of 5% (v/v) in autologous plasma, without further additives, is sufficient for cryopreservation of cord blood stem cells in a banking routine	[94]
	Prevents damage in hemopoietic stem cells, during cryopreservation	[95]
Other procedures	Presents a hydrogen-bound disruption action	[1]
	Due to its strong scavenging effects, it should be used with caution as a solvent in chemiluminescence studies. Concentrations below 1% (v/v) do not interfere with the results	[96]
	Enhances the penetration of chemicals and is added to fixatives to improve cell preservation. At low concentrations, in aldehyde and osmium-dichromate fixatives for electron microscopy, the ultrastructure and cellular details achieve good preservation	[97]
	At 1% (v/v), enhances the liposomal delivery of DNA to human breast tumor cells	[98]
	Decreases the *in vitro* binding of ethidium to DNA	[99]

4. Summary

Looking at the multitude of effects of DMSO brought out in this commentary, it is easily understood how many researchers working with DMSO (or studying one of its specific effects) can be unaware of the results of other groups working with it in a different context. The absence of a complete understanding of the effects of DMSO can preclude the reaching of accurate conclusions, since experimental artifacts caused by DMSO can lead to the erroneous interpretation of results. We believe that an increased awareness of the multidisciplinary utilization of this molecule in several research fields can be a valid contribution in order to avoid or minimize these problems.

Acknowledgments

This work was partially supported by the Fundação para a Ciência e Tecnologia (FCT) and by the Calouste Gulbenkian Foundation (Portugal).

References

[1] Santos NC, Prieto MJE, Morna-Gomes A, Betbeder D, Castanho MARB. Structural characterization (shape and dimensions) and stability of polysaccharide/lipid nanoparticles. Biopolymers 1997;41:511–20.
[2] Parkin J, Shea C, Sant GR. Intravesical dimethyl sulfoxide (DMSO) for interstitial cystitis—a practical approach. Urology 1997;49:105–7.
[3] Stout L, Gerspach JM, Levy SM, Yun SK, Lad PM, Leach GE, Zimmern PE. Dimethyl sulfoxide does not trigger urine histamine release in interstitial cystitis. Urology 1995;46:653–6.
[4] Burgess JL, Hamner AP, Robertson WO. Sulfhemoglobinemia after dermal application of DMSO. Int J Dermatol 1998;37:949–54.
[5] Wong CK, Lin CS. Remarkable response of lipoid proteinosis to oral dimethyl sulphoxide. Br J Dermatol 1988;119:541–4.
[6] Hsieh SD, Yamamoto R, Saito K, Iwamoto Y, Kuzuya T, Ohba S, Kobori S, Saito K. Amyloidosis presented with whitening and loss of hair which improved after dimethyl sulfoxide (DMSO) treatment. Jpn J Med 1987;26:393–5.
[7] McCammon KA, Lentzner NA, Moriarty RP, Schellhammer PF. Intravesical dimethyl sulfoxide for primary amyloidosis of the bladder. Urology 1998;52:1136–8.
[8] Iwasaki T, Hamano T, Aizawa K, Kobayashi K, Kakishita E. A case of pulmonary amyloidosis associated with multiple myeloma successfully treated with dimethyl sulfoxide. Acta Haematol 1994;91:91–4.
[9] Morassi P, Massa F, Mesesnel E, Magris D, D'Agnolo B. Treatment of amyloidosis with dimethyl sulfoxide (DMSO). Minerva Med 1989;80:65–70.
[10] Salim AS. Role of oxygen-derived free radical scavengers in the management of recurrent attacks of ulcerative colitis: a new approach. J Lab Clin Med 1992;119:710–7.
[11] Salim AS. Allopurinol and dimethyl sulfoxide improve treatment outcomes in smokers with peptic ulcer disease. J Lab Clin Med 1992;119:702–9.
[12] Salim AS. Oxygen-derived free-radical scavengers prolong survival in colonic cancer. Chemotherapy 1992;38:127–34.
[13] Salim AS. Role of oxygen-derived free radical scavengers in the treatment of recurrent pain produced by chronic pancreatitis. A new approach. Arch Surg 1991;126:1109–14.
[14] Salim AS. Protection against stress-induced acute gastric mucosal injury by free radical scavengers. Intensive Care Med 1991;17:455–60.
[15] Broadwell RD, Salcman M, Kaplan RS. Morphologic effect of dimethyl sulfoxide on the blood–brain barrier. Science 1982;217:164–6.
[16] Ikeda Y, Long DM. Comparative effects of direct and indirect hydroxyl radical scavengers on traumatic brain oedema. Acta Neurochir Suppl (Wien) 1990;51:74–6.
[17] Rosenstein ED. Topical agents in the treatment of rheumatic disorders. Rheum Dis Clin North Am 1999;25:899–918.
[18] Goto I, Yamamoto-Yamagushi Y, Honma Y. Enhancement of sensitivity of human lung adenocarcinoma cells to growth-inhibitory activity of interferon α by differentiation inducing agents. Br J Cancer 1996;74:546–54.

[19] Abdullaeva GK, Shakimova BSh. An evaluation of the efficacy of treating rheumatoid arthritis with preparations for local use. Revmatologiia (Mosk) 1989;4:35–9.
[20] Murav'ev IV. Treatment of rheumatoid synovitis by intra-articular administration of dimethyl sulfoxide and corticosteroid. Ter Arkh 1986;58:104–5.
[21] Shirley SW, Steward BH, Mirelman S. Dimethyl sulfoxide in treatment of inflammatory genitourinary disorders. Urology 1978;11: 215–20.
[22] Swanson BN. Medical use of dimethyl sulfoxide (DMSO). Rev Clin Basic Pharm 1985;5:1–33.
[23] Guerre P, Burgat V, Casali F. Le diméthylsulfoxyde (DMSO) usages experimentaux et toxicité. Rev Méd Vét 1999;150:391–412.
[24] Bertelli G, Gozza A, Forno GB, Vidili MG, Silvestro S, Venturini M, Del Mastro L, Garrone O, Rosso R, Dini D. Topical dimethyl sulfoxide for the prevention of soft tissue injury after extravasation of vesicant cytotoxic drugs: a prospective clinical study. J Clin Oncol 1995;13: 2851–5.
[25] Smith RS. A comprehensive macrophage-T-lymphocyte theory of schizophrenia. Med Hypotheses 1992;39:248–57.
[26] Kingery WS. A critical review of controlled clinical trials for peripheral neuropathic pain and complex regional pain syndromes. Pain 1997;73:123–39.
[27] Regelson W, Harkins SW. "Amyloid is not a tombstone"—a summation. The primary role for cerebrovascular and CSF dynamics as factors in Alzheimer's disease (AD): DMSO, fluorocarbon oxygen carriers, thyroid hormonal, and other suggested therapeutic measures. Ann NY Acad Sci 1997;826:348–74.
[28] Shibuya T, Murakawa M, Tsuda Y, Harada M. Successful treatment of primary amyloidosis with dimethyl sulfoxide and cytoreductive chemotherapy. Intern Med 1992;31:544–8.
[29] Bruck R, Shirin H, Aeed H, Matas Z, Hochman A, Pines M, Avni Y. Prevention of hepatic cirrhosis in rats by hydroxyl radical scavengers. J Hepatol 2001;35:457–64.
[30] Davis JM, Rowley SD, Braine HG, Piantadosi S, Santos GW. Clinical toxicity of cryopreserved bone marrow graft infusion. Blood 1990; 75:781–6.
[31] O'Donnell JR, Burnett AK, Sheehan T, Tansey P, McDonald GA. Safety of dimethyl sulphoxide. Lancet 1981;1:498.
[32] Samoszuk M, Reid ME, Toy PT. Intravenous dimethyl sulfoxide therapy causes severe hemolysis mimicking a hemolytic transfusion reaction. Transfusion 1983;23:405.
[33] Stroncek DF, Fautsch SK, Lasky LC, Hurd DD, Ramsay NKC, McCullough J. Adverse reactions in patients transfused with cryopreserved marrow. Transfusion 1991;31:521–6.
[34] Berenson RJ, Bensinger WI, Kalamasz D, Schuening F, Deeg HJ, Storb R. Avidin–biotin immunoadsorption. A technique to purify cells and its potential applications. In: Gale RP, Champlin R, editors. Progress in bone marrow transplantation. New York: Liss; 1987. p. 423.
[35] Smith DM, Weisenburger DD, Bierman P, Kessinger A, Vaughan WP, Armitage J. Acute renal failure associated with autologous bone marrow transplantation. Bone Marrow Transplant 1987;2:195–201.
[36] Hameroff SR, Otto CW, Kanel J, Weinstein PR, Blitt CD. Acute cardiovascular effects of dimethyl sulfoxide. Ann NY Acad Sci 1983;411:94–9.
[37] Styler MJ, Topolsky DL, Crilley PA, Covalesky V, Bryan R, Bulova S, Brodsky I. Transient high grade heart block following autologous bone marrow infusion. Bone Marrow Transplant 1992;10:435–8.
[38] Shlafer M, Matheny JL, Karow Jr AM. Cardiac chronotropic mechanisms of dimethyl sulfoxide: inhibition of acetylcholinesterase and antagonism of negative chronotropy by atropine. Arch Int Pharmacodyn Ther 1976;221:21–31.
[39] Rapoport AP, Rowe JM, Packman CH, Ginsberg SJ. Cardiac arrest after autologous marrow infusion. Bone Marrow Transplant 1991;7: 401–3.
[40] Baum CM, Weissman IL, Tsukamoto AS, Buckle AM, Peault B. Isolation of a candidate human hematopoietic stem cell population. Proc Natl Acad Sci USA 1992;89:2804–8.
[41] Pegg DE, Kemp NH. Collection, storage, and administration of autologous bone-marrow. Lancet 1960;2:1426–9.
[42] Jacob SW, Herschler R. Dimethyl sulfoxide after twenty years. Ann NY Acad Sci 1983;411:xiii–vii.
[43] Wolf P, Simon M. Dimethyl sulfoxide (DMSO) induced serum hyperosmolality. Clin Biochem 1983;16:261–2.
[44] Santos NC, Figueira-Coelho J, Saldanha C, Martins-Silva J. Biochemical, biophysical and haemorheological effects of dimethyl sulphoxide on human erythrocyte calcium loading. Cell Calcium 2002;31: 183–8.
[45] Franco RS, Weiner M, Wagner K, Martelo OJ. Incorporation of inositol hexaphosphate into red blood cells mediated by dimethyl sulphoxide. Life Sci 1983;32:2763–8.
[46] Zhang XQ, Eyzaguirre C. Effects of hypoxia induced by $Na_2S_2O_4$ on intracellular calcium and resting potential of mouse glomus cells. Brain Res 1999;818:118–26.
[47] Choi S-Y, Chae H-D, Park T-J, Ha H, Kim K-T. Characterization of high affinity neurotensin receptor NTR1 in HL-60 cells and its down regulation during granulocytic differentiation. Br J Pharmacol 1999;126:1050–6.
[48] Michel MC. Concomitant regulation of Ca^{2+} mobilization and G_{i3} expression in human erythroleukemia cells. Eur J Pharmacol 1998; 348:135–41.
[49] Reynaud D, Demin PM, Sutherland M, Nigam S, Pace-Asciak CR. Hepoxilin signaling in intact human neutrophils: biphasic elevation of intracellular calcium by unesterified hepoxilin A_3. FEBS Lett 1999;446:236–8.
[50] Böck M, Schleuning M, Heim UM, Mempel W. Cryopreservation of human platelets with dimethyl sulfoxide: changes in biochemistry and cell function. Transfusion 1995;35:921–4.
[51] Schirrmacher K, Büsselberg D, Langosch JM, Walden J, Winter U, Bingmann D. Effects of (±)-kavain on voltage-activated inward currents of dorsal root ganglion cells from neonatal rats. Eur Neuropsychopharmacol 1999;9:171–6.
[52] Wolosker H, Rocha JBT, Engelender S, Panizzutti R, De Miranda J, de Meis L. Sarco/endoplasmic reticulum Ca^{2+}-ATPase isoforms: diverse response to acidosis. Biochem J 1997;321:545–50.
[53] Ogura T, Shuba LM, McDonald TF. Action potentials, ionic currents and cell water in guinea pig ventricular preparations exposed to dimethyl sulfoxide. J Pharmacol Exp Ther 1995;273:1273–86.
[54] Benaim G, de Meis L. Activation of the purified erythrocyte plasma membrane Ca^{2+}-ATPase by organic solvents. FEBS Lett 1989;244: 484–6.
[55] Lehotský J, Raeymaekers L, Casteels R. Effects of dimethyl sulfoxide and polycationic neomycin on stimulation of purified plasma membrane Ca^{2+}-pump by negatively charged phospholipids. Gen Physiol Biophys 1992;11:567–77.
[56] McConnell EJ, Wagoner MJ, Keenan CE, Raess BU. Inhibition of calmodulin-stimulated ($Ca^{2+} + Mg^{2+}$)-ATPase activity by dimethyl sulfoxide. Biochem Pharmacol 1999;57:39–44.
[57] DeForge LE, Fantone JC, Kenney JS, Remick DG. Oxygen radical scavengers selectively inhibit interleukin 8 production in human whole blood. J Clin Invest 1992;90:2123–9.
[58] Saeed SA, Karimi SJ, Suria A. Differential effects of dimethyl sulfoxide on human platelet aggregation and arachidonic acid metabolism. Biochem Med Metab Biol 1988;40:143–50.
[59] Matthews GL, Engler SJ, Morris EA. Effect of dimethyl sulfoxide on articular cartilage proteoglycan synthesis and degradation, chondrocyte viability, and matrix water content. Vet Surg 1998;27: 438–44.
[60] Smith CL, Macdonald MH, Tesch AM, Willits NH. In vitro evaluation of the effect of dimethyl sulfoxide on equine articular cartilage matrix metabolism. Vet Surg 2000;29:347–57.

[61] Chang CK, Albarillo MV, Schumer W. Therapeutic effect of dimethyl sulfoxide on ICAM-1 gene expression and activation of NF-κB and AP-1 in septic rats. J Surg Res 2001;95:181–7.
[62] He B, Monick MM, Hunninghake GW. The effect of dimethyl sulfoxide on activation of the major immediate early promoter of human cytomegalovirus. Chin Med J 1998;111:712–7.
[63] Kelly KA, Hill MR, Youkhana K, Wanker F, Gimble JM. Dimethyl sulfoxide modulates NF-κB and cytokine activation in lipopolysaccharide-treated murine macrophages. Infect Immun 1994;62:3122–8.
[64] Schick BP, Senkowski-Richardson S. Proteoglycan synthesis in human erythroleukaemia (HEL) cells. Biochem J 1992;282:651–8.
[65] Sekizuka E, Benoit JN, Grisham MB, Granger DN. Dimethyl sulfoxide prevents chemoattractant-induced leukocyte adherence. Am J Physiol 1989;256:H594–7.
[66] Thomas CP, Dunn MJ, Mattera R. Ca^{2+} signalling in K562 human erythroleukaemia cells: effect of dimethyl sulphoxide and role of G-proteins in thrombin and tromboxane A_2-activated pathways. Biochem J 1995;312:151–8.
[67] Teraoka H, Sawai M, Takase K, Yamamoto K, Nozaki N, Okazaki T, Tsukada K. Expression of c-*fos* and c-*myc* in Raji Burkitt's lymphoma cells during the progression of DMSO-induced G1 cells into S phase. Exp Cell Res 1991;195:274–6.
[68] Darling D, Tavassoli M, Linskens MH, Farzaneh F. DMSO induced modulation of c-*myc* steady-state RNA levels in a variety of different cell lines. Oncogene 1989;4:175–9.
[69] Srinivas S, Sironmani TA, Shanmugam G. Dimethyl sulfoxide inhibits the expression of early growth-response genes and arrests fibroblasts at quiescence. Exp Cell Res 1991;196:279–86.
[70] Sawai M, Takase K, Teraoka H, Tsukada K. Reversible G1 arrest in the cell cycle of human lymphoid cell lines by dimethyl sulfoxide. Exp Cell Res 1990;187:4–10.
[71] Teraoka H, Mikoshiba M, Takase K, Yamamoto K, Tsukada K. Reversible G1 arrest induced by dimethyl sulfoxide in human lymphoid cell lines: dimethyl sulfoxide inhibits IL-6-induced differentiation of SKW6-CL4 into IgM-secreting plasma cells. Exp Cell Res 1996;222:218–24.
[72] Kumakura S, Ishikura H, Tsumura H, Hayashi H, Endo J, Tsunematsu T. c-*myc* protein expression during cell cycle phases in differentiating HL-60 cells. Leuk Lymphoma 1994;14:171–80.
[73] Toren A, Rechavi G. What really cures in autologous bone marrow transplantation? A possible role for dimethyl sulfoxide. Med Hypotheses 1993;41:495–8.
[74] Collins SJ, Ruscetti FW, Gallagher RE, Gallo RC. Terminal differentiation of human promyelocytic leukemia cells induced by dimethyl sulfoxide and other polar compounds. Proc Natl Acad Sci USA 1978;75:2458–62.
[75] Isom HC, Secott T, Georgoff I, Woodworth C, Mummaw J. Maintenance of differentiated rat hepatocytes in primary culture. Proc Natl Acad Sci USA 1985;82:3252–6.
[76] Divecha N, Letcher AJ, Banfic HH, Rhee S, Irvine RF. Changes in the components of a nuclear inositide cycle during differentiation in murine erythroleukaemia cells. Biochem J 1995;312:63–7.
[77] Liu J, Yoshikawa H, Nakajima Y, Tasaka K. Involvement of mitochondrial permeability transition and caspase-9 activation in dimethyl sulfoxide-induced apoptosis of EL-4 lymphoma cells. Int Immunopharmacol 2001;1:63–74.
[78] Lin CK, Kalunta CI, Chen FS, Nguyen TT, Kaptein JS, Lad PM. Dimethyl sulfoxide suppresses apoptosis in Burkitt's lymphoma cells. Exp Cell Res 1995;216:403–10.
[79] Sakuragawa N. Medicinal therapy for lysosomal storage diseases. Nippon Rinsho 1995;53:3072–6.
[80] Bell FP. Transfer of cholesterol between serum lipoproteins, isolated membranes, and intact tissue. Exp Mol Pathol 1973;19:293–303.
[81] Herzmann E. Studies of the effect of dimethyl sulfoxide on experimental hypercholesteremia in young cocks. Acta Biol Med Ger 1968;20:483–7.
[82] Mackie EJB, Dwyer NK, Vanier MT, Sokol J, Merrick HF, Comly ME, Argoff CE, Pentchev PG. Type C Niemann-Pick disease: dimethyl sulfoxide moderates abnormal LDL-cholesterol processing in mutant fibroblasts. Biochim Biophys Acta 1989;1006:219–26.
[83] Alam SS, Layman DL. Dimethyl sulfoxide as a cholesterol-lowering agent in cultured fibroblasts exposed to low density lipoproteins. Biochim Biophys Acta 1982;710:306–13.
[84] Maehara M, Yagita M, Isobe Y, Hoshino T, Nakagawara G. Dimethyl sulfoxide (DMSO) increases expression of sialyl Lewis x antigen and enhances adhesion of human gastric carcinoma (NUGC4) cells to activated endothelial cells. Int J Cancer 1993;54:296–301.
[85] Ryan JJ, Clarke MF. Alteration of p53 conformation and induction of apoptosis in a murine erythroleukemia cell line by dimethyl sulfoxide. Leuk Res 1994;18:617–21.
[86] Hanspal M, Prchal JT, Palek J. Biogenesis of erythrocyte membrane skeleton in health and disease. Stem Cells 1993;11:8–12.
[87] Sato K, Han DC, Ozawa M, Fujii Y, Tsushima T, Shizume K. Dimethyl sulfoxide maintains human thyroid cells in suspension culture, facilitating synthesis and release of thyroid hormone. Biochem Biophys Res Commun 1988;155:100–5.
[88] Wu RM, Mohanakumar KP, Murphy DL, Chiueh CC. Antioxidant mechanism and protection of nigral neurons against MPP^+ toxicity by deprenyl (selegiline). Ann NY Acad Sci 1994;738:214–21.
[89] Ogura T, Kasamaki Y, McDonald TF. Force-relaxant actions of dimethyl sulfoxide on guinea-pig and rabbit papillary muscles. J Mol Cell Cardiol 1996;28:1777–88.
[90] Nygren P, Larsson R, Rastad J, Akerstrom G, Gylfe E. Dimethyl sulfoxide increases cytoplasmic Ca^{2+} concentration and inhibits parathyroid hormone release in normal bovine and pathological human parathyroid cells. Biochim Biophys Acta 1987;928:194–8.
[91] Jezek D, Schulze W, Kalanj-Bognar S, Vukelic Z, Milavec-Puretic V, Krhen I. Effects of various cryopreservation media and freezing–thawing on the morphology of rat testicular biopsies. Andrologia 2001;33:368–78.
[92] Lakey JR, Anderson TJ, Rajotte RV. Novel approaches to cryopreservation of human pancreatic islets. Transplantation 2001;72:1005–11.
[93] Fu T, Guo D, Huang X, O'Gorman MR, Huang L, Crawford SE, Soriano HE. Apoptosis occurs in isolated and banked primary mouse hepatocytes. Cell Transplant 2001;10:59–66.
[94] Richter E, Eichler H, Raske D, Leveringhaus A, Zieger W, Kerowgan M, Goldmann SF. 5% Me_2SO is sufficient to preserve stem cells derived from cord blood. Bone Marrow Transplant 1998;22(Suppl 1): S16.
[95] Egorin MJ, Rosen DM, Sridhara R, Sensenbrenner L, Fox MC. Plasma concentrations and pharmacokinetics of dimethyl sulfoxide and its metabolites in patients undergoing peripheral blood stem cell transplants. J Clin Oncol 1998;16:610–5.
[96] Kahler CP. Evaluation of the use of the solvent dimethyl sulfoxide in chemiluminescent studies. Blood Cells Mol Dis 2000;26:626–33.
[97] Fassel TA, Sohnle PG, Kushnaryov VM. The use of dimethyl sulfoxide for fixation of yeasts for electron microscopy. Biotech Histochem 1997;72:268–72.
[98] Jain PT, Gewirtz DA. Enhancement of liposomal gene delivery in human breast cancer cells by dimethyl sulfoxide. Int J Mol Med 1998;1:609–11.
[99] Kimura H, Aoyama T. Decrease in sensitivity to ethidium bromide by caffeine, dimethyl sulfoxide or 3-aminobenzamide due to reduced permeability. J Pharmacobiodyn 1989;12:589–95.