Implications of Dibenzyl Trisulphide for Disease Treatment Based on its Mode of Action

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ABSTRACT

Studies conducted on the secondary metabolite (natural product), dibenzyl trisulphide (DTS), which was isolated from the sub-tropical shrub Petiveria alliacea *(guinea hen weed, anamu) [Phytolaccaceae] have shown tremendous pharmaceutical promise as a drug prototype. This is now reflected in the development of the broad spectrum anti-cancer molecule, fluorapacin (bis(4-fluorobenzyl) trisulphide) which has an excellent safety profile. The mode of action elucidated for DTS is the mitogen activated protein extracellular regulated kinases 1 and 2 (MAPKinases ERK 1 and ERK 2). The MAPKinase signal transduction biochemical pathways are important in the regulation of a wide range of cellular processes which are important in disease establishment. These processes include: cancer cell proliferation, nerve repair, memory enhancement, autoimmune diseases, which are linked to thymic cell involution and bone marrow functions, cerebrovascular and cardiovascular diseases. In addition to the MAPkinase signal transduction mode of action, DTS also prevents the denaturation of serum albumin which is a feature of nonsteroidal anti-inflammatory drugs, thus supporting the molecule's possible role in the treatment of inflammatory ageing diseases.*

Implicaciones del Trisulfuro de Dibencilo para el Tratamiento de Enfermedades a Partir de su Modo de Acción

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RESUMEN

Los estudios realizados sobre el metabolito secundario (producto natural), trisulfuro de dibencilo (TSD), que fue aislado del arbusto subtropical Petiveria alliacea *(hierba de guinea, anamú) [Phytolaccaceae] muestran que se trata de una tremenda promesa farmacéutica como prototipo de droga. Esto se refleja actualmente en el desarrollo de la molécula anticancerígena de amplio espectro, la fluorapacina (bis (4-fluorobencilo) trisulfuro) que posee un excelente perfil de seguridad. El modo de acción para el TSD se explica partiendo de las proteínas quinasas 1 y 2 activadas por mitógenos y reguladas por señales extracelulares (Quinasas MAP ERK 1 y ERK 2). Las vías bioquímicas de transducción de la señal de la quinasa MAP, son importantes en la regulación de una amplia variedad de procesos celulares, importantes a la hora de determinar una enfermedad. Dichos procesos comprenden: la proliferación de la célula cancerosa, la reparación de nervios, el mejoramiento de la memoria, y las enfermedades autoinmunes, vinculadas con la involución tímica y las funciones de la médula, las enfermedades cerebrovasculares y cardiovasculares. Además del modo de acción de las transducción de señales de la quinasa MAP, el TSD previene también la desnaturalización de la albúmina sérica, lo cual constituye una característica de las drogas anti-inflamatorias no esferoidales,*

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apoyando así el posible papel de las moléculas en el tratamiento de las enfermedades inflamatorias en el proceso de envejecimiento.

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INTRODUCTION

As the medicinal potential of the polysulphide, dibenzyl trisulphide (DTS) and its synthetic derivatives (1, 2) unfolds, it would appear that the molecules may have tremendous potential in the treatment of a wide range of diseases (2, 3). Small molecules like DTS with a signal transduction mode of action, such as the mitogen activated protein kinases (MAPKinases) are preferred for drug development. These small signal transduction molecules are less toxic than conventional therapeutic drugs (4). The MAPKinase signal transduction biochemical pathway regulates a wide range of biological processes *eg* cancer cell proliferation, nerve repair, memory, autoimmune diseases, cerebrovascular, cardiovascular and ageing related diseases. Thus, when small molecules having MAPKinase signal transduction mode of action are found, it is critical that they be evaluated for their broad spectrum therapeutic value in order to validate their significance. Thus, we hereby propose that in addition to the anti-proliferation/cytotoxic (5), thymic cell proliferation (3, 6) and bone marrow stimulation (as revealed by elevation of thrombocyte and granulocyte counts) studies conducted to date (3, 6), nerve repair, memory enhancement, cardiovascular and anti-ageing assessments be performed on DTS since these processes are regulated by the MAPKinase signal transduction pathway.

Neuron regeneration and nerve repair

Williams *et al* (2) have proposed that DTS may have implications in neuron regeneration and nerve repair since MAPKinase phosphorylation emerging from tyrosine residue situated on axons is one of the processes implicated (7). Activation of extracellular signal-regulated kinase (ERK), a member of the mitogen-activated protein kinase (MAPK) family has been proposed to mediate neurite out-growth-promoting effects of several neurotrophic factors *in vitro* (8).

Activation of bone marrow stromal cell leading to the production of endothelial progenitor cells

In recent years, research findings have revealed that endothelial progenitor cells (EPCs) originating from bone marrow could be important in the management of cerebrovascular diseases such as strokes (9) and cardiovascular diseases *eg* pulmonary hypertension (10), myocardial infarction (11), peripheral limb ischaemia (12) and repair to damaged vessels (10). In addition, diabetes, a major condition associated with cardiovascular diseases, also adversely affects endothelial cell function and numbers (13, 14).

The activation of human bone marrow stromal cells (mesenchymal cells) leading to the production of endothelial progenitor cells is possible via chemokine receptor ligand binding that trigger phosphorylation of MAPKinase -ERK 1 and ERK 2 signal transduction pathway (15, 16) which is the mode of action elucidated for DTS (5). Thus, it is plausible to state that DTS could be useful in treating diseased conditions that can be ameliorated using endothelial progenitor cells if the molecule is found to upregulate their release from the bone marrow. This is suggested based on the fact that DTS elevates the release of granulocyte and thrombocyte counts (3, 6) which are linked to bone marrow activation.

Anticancer

Since the discovery of the role of Ras oncogenes in cancer research, an explosion of research has occured in the area of signal transduction (4). In an effort to understand how Ras transmits extracellular growth signals, the MAPKinase pathway has emerged as the crucial route between membrane-bound Ras and the nucleus. The MAPKinase cascade presents novel opportunities for the development of new cancer therapies *eg* DTS (4, 5) with less toxicity than conventional chemotherapeutic drugs (4).

Activation of the thymus upon involution

Dibenzyl trisulphide stimulates the production of thymocytes (thymic cells) in involuted thymus in mice (3, 6). During involution, the thymus shows a decrease in size, decreased cellularity, decline in the production of new cells from the bone marrow, decline in responsiveness to vaccines and increased incidence in autoimmune diseases (17, 18). The activation (proliferation) of thymic cells is reported to be regulated via the MAPKinase signal transduction pathways (19, 20). Thus, if DTS is capable of re-activating thymic cell upon involution, it could play a major role in the treatment of diseases that are linked to ageing and involution of the thymus.

CONCLUSION

Dibenzyl trisulphide (DTS) and its derivatives seem to be an emerging therapeutic group of agents, especially in cancer research. However, the mode of action (MAPKinase signal transduction) elucidated for DTS suggests that the molecule could play a major role in the treatment of other diseases.

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