COLCHICINE IN THE THERAPY OF CARDIOVASCULAR DISEASE: THE BULGARIAN CONTRIBUTION

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ABSTRACT

Over the past decades, advances in the knowledge of colchicine about its mechanisms of cellular actions have led to potential new uses for this very old drug. Here, I present briefly the Bulgarian contribution to possible potential of microtubule-disassembling agents (antitubulins), such as colchicine, in the therapy of various cardiovascular diseases such as atherosclerosis, atrial fibrillation, pericarditis, cardiac hypertrophy-associated heart failure, and systemic necrotizing vasculitis. *Scr Sci Med.* 2017;49(4):83-85

Keywords: *colchicine, microtubules, antitubulins, cardiovascular disease, inflammation, fibrosis*

INTRODUCTION

The saga of *Colchicum autumnale* (commonly known as autumn crocus, meadow saffron or naked ladies), from which colchicine was extracted, has been around for some 3 000 years, as described by ancient writers as the remedy of choice for gout patients suffering debilitating pain due to acute arthritis. Today, this therapeutic effect is known to be due to its anti-inflammatory action. However, in the last 30-40 years colchicine has also been used to treat familial Mediterranean fever (and related amyloidosis and recurrent pericarditis), Behçet's disease, acute febrile neutrophilic dermatosis (Sweet's syndrome), epidermolysis bullosa acquisita, leukocytoclastic vasculitis, aphthous stomatitis, also liver cirrhosis, scleroderma and other fibro-inflammatory diseases (1,2).

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Microtubules and colchicine

Cytoplasmic and spindle microtubules (MT) are 25 nm in diameter cytoskeletal structures composed of self-assembling dimers of α -tubulin and β -tubulin in collaboration with various MAP (MT-associated proteins). Colchicine binds to β -tubulin, resulting in the inhibition of MT formation and/or disassembly of preformed MT. In effect, colchicine-sensitive processes are (i) for interphase cells, protein secretion (1-10), migration, inflammasome-mediated inflammation, receptor-mediated signaling, and (ii) for mitotic cells, proliferation, this latter effect being out of the scope of the present article.

The Bulgarian contribution

The concept of possible therapeutic potential of MT-disassembling agents (antitubulins), such as colchicine, has emerged in the Laboratory of Electron Microscopy, Department of Anatomy and Histology, Medical Institute, Varna, Bulgaria, studying the secretory function of vascular smooth muscle cells (3,4,6-10). Preliminary proof from data on the new concept was presented in a lecture delivered by the author at the International Symposium on Smooth Muscle of the Artery, held Heidelberg, Germany, October 1973, which was published in 1975 (3; see related papers in 1,4-15).

From this time onward, the antitubulin concept has fully supported up to date (16-25). It has also been demonstrated that excess MT density is important for myocardial contractile dysfunction, suggesting that this may be one mechanism contributing to the development of heart failure due to cardiac hypertrophy. It appears that colchicine may restore the contractile activity of cardiomyocytes (26,27).

CONCLUSION

The effectiveness of low-dose colchicine (referred to as LoDoCo) - oral colchicine at subantimitotic doses of 0.5-1.0 mg/daily - could become one of the breakthroughs in cardiovascular translational research. Further experimental and clinical studies will definitely be required before gaining real confidence in this kind of antitubulin therapy in cardiovascular disease. Colchicine is simply an example of this approach, which may lead to developing new and more specific drugs with anti-inflammatory and anti-fibrotic effects in cardiovascular disease, including coronary reocclusion after angioplasty and coronary artery bypass grafting.

However, we must recall Robert Frost's refrain:

*WE DANCE ROUND IN A RING AND
SUPPOSE,*

*BUT THE SECRET SITS IN THE MIDDLE
AND KNOWS.*

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