Development of anti-atherosclerotic drugs on the basis of cell models or how to make the elderly pay for placebos

The large research series has become internationally known in 1986 after a publication by the ex-Soviet minister of health as the first author and continues until today. In brief, cell cultures have been used for evaluation of the ability of different substances to enhance or diminish cholesterol accumulation by cultured cells, which has been interpreted as anti- or pro-atherogenic action. The following was reported: after 24 hours of incubation with diluted sera from patients with coronary atherosclerosis, the content of cholesterol in the cultured cells increased 2 to 5 times. Incubation with sera from healthy people did not induce cholesterol accumulation. Such striking difference appears doubtful. According to a personal communication at the 77th Congress of the European Atherosclerosis Society, the “cell cultures” did not grow. Therefore, it would be correct to name these cells, surviving for several days or weeks in serum-containing media, not cell cultures but incubated cells. Using the same model, various drugs and natural substances were found to possess pro- or anti-atherogenic potencies. If a substance induced lipid accumulation by the cultured cells it was regarded to be atherogenic and vice versa. However, as discussed previously, if a drug lowers the uptake of lipids by cells in a culture, it should be expected to increase the blood cholesterol level in vivo. So, in familial hypercholesterolemia and some other diseases, an abnormality of lipoprotein receptors, associated with a decreased cholesterol uptake by cells from blood, results in accelerated atherosclerosis. The blood level of atherogenic lipoproteins largely depends on the functioning receptors.

In cultures, many cells rely on the receptors for cholesterol supply. It can be reasonably assumed that a drug, supposedly acting upon blood atherogenicity , or through receptor-mediated mechanisms, inhibiting cholesterol uptake by cultured cells, would elevate the blood cholesterol level in vivo. By analogy with familial hypercholesterolemia, it can contribute to atherosclerosis: lipids would be deposited into the intercellular substance of the vascular wall, in vulnerable sites with the damaged endothelial barrier or into pre-existent atherosclerotic plaques – so as it happens in conditions of progressive atherosclerosis. This is the philosophical paradox disregarded by Professor Orekhov and co-workers: the substances supposedly having an “anti-atherogenic” potency in a cell culture might reduce cholesterol uptake diffusely by entire cell populations contributing to hypercholesterolemia. On the contrary, atherosclerosis is a focal disease, affecting primarily damaged sites of the vascular lining, which would be favored by hypercholesterolemia.

In conclusion, the use of cultures or incubated cells for prediction of body responses is limited; and results of such experiments should not be directly extrapolated onto patients. Nonetheless, the cell models have been used since the last 30 years for testing of supposedly anti-atherogenic drugs and food supplements, for their official registration and obtaining permissions for practical use. Research quality and possible influence by the industry should be taken into account defining inclusion criteria for studies into reviews. Scientifically inadequate methods can be used for the purpose of official registration of drugs and dietary supplements. As a result, drugs with unproven

effects can be offered to the elderly and other patients misinformed not only by advertising but also by some publications supposed to be scientific.

Publication

Orekhov`s Method: Reassessment of In vitro Lipid Uptake Assays.
Jargin SV
Recent Pat Cardiovasc Drug Discov. 2015