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Mini-Review

Aortic Aneurysm: Insight into Potential Therapeutic Agents against the Disease

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Abstract

An aneurysm is localized dilatation of larger blood vessels as a result of regional weakening of the wall structure. Aortic aneurysm is an irreversible dilation of the aorta involving all the three wall layers: the inner elastic layer or intima, the middle or subendothelial connective tissue layer, and the external layer or adventitia. Aortic aneurysm is classified into abdominal or thoracic aortic aneurysm. The risk factors are atherosclerosis (hardened arteries), high blood pressure, high blood cholesterol and smoking. Prophylactic surgical repair is the current management of aortic aneurysms. Potential therapeutic agents that stop or reduce aortic aneurysm progression have been investigated. Their biological effects depend on stabilization of growing aortic aneurysms, intervention on the pathway of the activated inflammatory and proteolytic processes that tend to enlarge aortic aneurysms.

Introduction

Aneurysm is a localized or diffuse dilatation of the blood vessel wall with a diameter at least 1.5 times its normal caliber [1]. It is generally linked with rupture and a life-threatening hemorrhage. Aneurysms mostly occur within arterial wall. The aorta is the main artery that carries oxygen-rich blood away from the heart through the chest to the rest of the body. Aortic aneurysm is an irreversible dilation of the aorta (a balloon-

like bulge in the aorta), involving all three walls. As a result of the force of blood pumping against the wall, aortic aneurysms can dissect (leak blood in between the split layers of the artery wall) or rupture (completely burst causing bleeding inside the body).

Aortic aneurism is classified into abdominal (most common) or thoracic aortic aneurysm, generally on the basis of anatomic location, morphologic shape namely fusiform (spindle-shaped) or saccular (small sac or cyst) and size [2].

The disease is mostly caused by atherosclerosis. Aortitis (infective and inflammatory), cystic medial necrosis and hemodynamic alterations (such as aortic stenosis, regurgitation) are other causes of aortic aneurysm [3]. The symptoms may include (i) pain in the jaw, neck, upper back or chest, coughing, hoarseness or difficult breathing for thoracic aortic aneurysm and (ii) pulsating enlargement or tender mass, or pain in the back, abdomen, or groin that is not relieved with analgesics or position change for abdominal aortic aneurysm [4]. Aortic aneurysm may be diagnosed when the ascending aortic diameter is 5 cm or more, and the descending thoracic aortic diameter is 4 cm or more [5].

Diagnosis is aided by results of chest X-ray, computer tomography of the aorta, transthoracic echocardiogram (ultrasound of the heart chamber and valves) or transthoracic echocardiogram (ultrasound of the thoracic aorta).

Treatment

The current management of aortic aneurysms is mostly by prophylactic surgical repair. However, a number of potential therapeutic agents that stop or reduce aortic aneurysm progression and therefore alleviate or postpone the need for surgical repair are being explored. Such potential therapeutic agents are:

Angiotensin Converting Enzyme (ACE) Inhibitors and Angiotensin II Receptor Antagonists (ARBS):

These two classes of therapeutic agents were investigated against aortic aneurysm in experimental animal models. The results showed that ACE inhibitors and ARBs prevented rupture of the internal elastic lamina of the aorta. Their effects were limited to angiotensin II and not other parts of the renin/angiotensin system [6,7]. Typical examples of these potential therapeutic agents are enalapril, irbesartan, losartan, and temisartan.

(ii) Beta Blockers:

Hypertension has been shown to increase the development of aneurysms in animal model. Beta blockers have been investigated for their biological activities against aortic aneurysm because they can successfully treat hypertension. The findings suggest that these agents slow aneurysm progression in both experimental animal models and retrospective studies of patients with abdominal aortic aneurysm [8], Typical examples of beta blockers are propranolol and atenolol.

(iii) Matrix Metalloproteinase (MMP) Inhibition:

An imbalance between MMP-9 and their naturally occurring inhibitors has been reported in aortic aneurysm suggesting that active substances capable of inhibiting the activity of these enzymes could act as therapeutic agents against aortic aneurysm. Experimental results show these chemical substances to have effective anti-MMP properties [9]. Typical examples of these potential therapeutic agents are indomethacin, doxycycline and roxithromycin.

(iv) Nonsteroidal Anti-Inflammatory Agents:

These therapeutic agents have been reported to reduce aneurysm growth in animal models as well as in human aortic aneurysmal tissue [10]. Typical examples of these potential therapeutic agents are indomethacin and acetylsalicyclic acid.

(v) Anti-chlamydial Therapy

The hypothesis stating that atherosclerosis may have an infective etiology as well as sharing the same risk factors with abdominal aortic aneurysm necessitated the investigation of treating abdominal aortic aneurysm with anti-chlamydial therapy [11]. Typical example of the potential therapeutic agent is roxithromycin.

(vi) HMG Co-A Reductase Inhibitors (statins)

Experimental data in human beings using statins (based on their clinical applications) have shown good results in aneurysms and peripheral vascular disease [12]. These findings suggest that all patients with aortic aneurysms should be on statin therapy if tolerated. Their actions might involve reducing aortic inflammation and proteolysis [13]. Typical examples of such potential therapeutic agents are simvastatin and flaviststin.

(vii) Signalling Pathways Inhibitors:

Signalling pathways inhibition has been reported to provide regression of established experimental aneurysms [14,15]. These agents have the ability to inhibit Jun N-terminal kinase [JNK] and nuclear factor kappaB [NFkB] respectively and have been found to be effective in reducing aneurysm formation in the experimental studies [16]. Typical example of such a potential therapeutic agent is rosiglitazone.

In addition to these potential therapeutic agents, other therapeutic agents that had been studied as potential active agents for the management of aortic aneurysms are fenofibrate, ticagrelor, eperenone, inositol and metformin.

Conclusion

Aortic aneurysms either of the abdominal or thoracic type contributes immensely to morbidity and mortality in human population mainly because the majority of them are asymptomatic and therefore often remain undetected. The consequences of aortic aneurysm are (i) aortic dissection- a tear in the inner aortic layer that

leads to further separation of the inner and middle layers of the wall of the aorta following influx of blood or (ii) rupture- a complete tear through all three layers of the aorta. Research works towards obtaining potential therapeutic agents against aortic aneurysms are based on targeting one of the specific processes that have been observed to influence aneurysm development. Biological events responsible for aortic aneurysms are recruitment of inflammatory cells, activation of MMPs and production of reactive oxygen species. Inhibition of signalling pathways (JNK and NFκB) has resulted in regression of aortic aneurysms. Finally, clinical therapeutic agents could soon emerge from these potential therapeutic agents thus making patients not to be limited to only surgery

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