INHIBITION OF O-6-METHYLGUANINE-DNA METHYLTRANSFERASE INDUCES CELLULAR SENESCENCE AND RELAXATORY DYSFUNCTION IN SMOOTH MUSCLE OF RAT AORTA

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Cellular senescence is characterized by irreversible cell cycle arrest that is accompanied by morphological and physiological changes. Senescent cells accumulate in tissues during ageing and contribute to increased risk of developing age-related cardiovascular diseases such as atherosclerosis or hypertension. Cellular senescence is closely linked to DNA damage. Recently we discovered that the inhibition of DNA repair through O-6-methylguanine-DNA methyltransferase (MGMT) by O-6-benzylguanine (BG) induces cellular senescence in vascular smooth muscle cells and we decided to confirm our results on animal model.

Wistar rats were administered with p.o. BG in dose 12mg/kg (2 doses within 24hours). After 12 weeks rats were sacrificed, aorta was removed and prepared for vascular measurements and for determination of protein expression involved in cellular senescence.

After the treatment we observed significantly lower relaxatory response of aorta to sodium nitroprusside. Moreover, we observed significantly increased expression of $p21^{Cip1}$ and $p27^{Kip1}$ that are typical markers of senescence. Furthermore, we observed significant increase of MAPK signaling protein p38 that can mediate cellular senescence and control expression of $p21^{Cip1}$.

Based on these results, we conclude that inhibition of MGMT induced cellular senescence in vascular smooth muscle of aorta through $p21^{Cip1}$ and $p27^{Kip1}$ and this could cause decreased relaxatory ability. Furthermore, elevated MAPK protein p38 could be behind mentioned changes and drive cellular senescence in this model.

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