

# DIFFERENTIAL SEX RESPONSE TO ASPIRIN IN DECREASING ANEURYSM RUPTURES IN HUMANS AND MICE

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**W**e previously found that aspirin decreases the risk of cerebral aneurysm rupture in humans. We aim to assess whether a sex differential exists in the response of human cerebral aneurysms to aspirin and confirm these observations in a mouse model of cerebral aneurysm. A nested case-control analysis from the international study of unruptured intracranial aneurysms was performed to assess whether a sex differential exists in the response of human cerebral aneurysms to aspirin. A series of experiments were subsequently performed in a mouse model of cerebral aneurysms. Aneurysms were induced with hypertension and elastase injection into mice basal cisterns. We found that aspirin decreased the risk of aneurysm rupture more significantly in men than in women in the International Study of Unruptured Intracranial Aneurysms. In mice, aspirin and cyclooxygenase-2 inhibitor did not affect cerebral aneurysm formation but significantly decreased the incidence of rupture. The incidence of rupture was significantly lower in male versus female mice on aspirin. Gene expression analysis from cerebral arteries showed higher 15-hydroxyprostaglandin dehydrogenase levels in male mice. The rate of cerebral aneurysm rupture was similar in male mice receiving aspirin and 15-hydroxyprostaglandin dehydrogenase inhibitor compared with females receiving aspirin and 15-hydroxyprostaglandin dehydrogenase agonist, signaling a reversal of the sex-differential response to aspirin. Aspirin decreases aneurysm rupture in human and mice, in part through cyclooxygenase-2 pathways. Evidence from animal and human studies suggests a consistent differential effect by sex. 15-hydroxyprostaglandin dehydrogenase activation in females reduces the incidence of rupture and eliminates the sex-differential response to aspirin.

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