Testing Dopamine for Treatment of Cerebral Vasospasm After Subarachnoid Hemorrhage Using an In Vitro Model.

Matthew Cooper, Joseph F. Clark, and Gail J. Pyne-Geithman.
Dept. of Neurology

Introduction: Cerebral vasospasm (CV) is a significant cause of mortality (11,000 per year in the US) and morbidity in patients surviving a subarachnoid hemorrhage (SAH). Onset of CV occurs 3-10 days after the SAH, and this affords a valuable therapeutic window. There are currently no effective therapies for this debilitating pathology. The aim of our study was to determine the possible efficacy of dopamine therapy in vitro in preventing or reversing smooth muscle contraction during CV after SAH. We hypothesized that stimulation of the nitric oxide synthase (NOS) pathway via dopaminergic receptor activation may be an effective way to prevent or reverse cerebral vasospasm after subarachnoid hemorrhage. Methods: Sections of porcine internal carotid arteries (0.5 mm in length) were placed in a water-jacketed organ bath (physiological saline solution, pH 7.4 @ 37°C) and isometric force measured. KCl-induced contraction was set as 100% contraction (Fmax) and the contractile response of the arteries under various conditions was compared to Fmax. In vitro vasospasm was induced using cerebrospinal fluid from patients who suffered CV after SAH (CSFV). Arteries were treated with dopamine (10µm) both before and after addition of CSFV. Selected dopamine antagonists (L-SPD vs. D1 receptors, haloperidol vs. D2, U99194A vs. D3) were used to determine through which receptor dopamine was having its effects on the CV in vitro. Immunohistochemical staining for both inducible and endothelial NOS (iNOS and eNOS) of these arterial rings was performed. Results: Both pretreatment and posttreatment with dopamine reduced the vasoconstriction caused by CSFV significantly (70% ± 9%, 36% ± 5% of Fmax, respectively). Blockade of D2 receptors with haloperidol abolished this effect, whereas the D1 and D3 antagonists did not. Immunohistochemical staining suggests that the mechanism of dopamine’s action here includes induction of iNOS in the smooth muscle layers of the arteries. Conclusions and Significance: Our data suggests that the effects elicited by dopamine against vasospasm were mediated by D2 receptors. This statistically significant, in vitro data may be used to develop clinical therapies of dopamine D2 receptor agonists for use as a treatment for CV after SAH. This could add an important weapon to the armory of the neurosurgeon, for a pathology where current therapies are inconsistent and moderately effectual at best.