Prostaglandin E2 (PGE2) is an important mediator of inflammation in various cell types and it is known to cause neurotoxicity as well as neuroprotection in models of stroke and excitotoxicity. The contradictory effects of PGE2 on cell survival and inflammation result from its action on four receptors (EP1-4) with distinct signal transduction profiles and different impact on cell viability. In the present study, we show that inactivation of the EP1-receptor or activation of the EP4-receptor reduces infarct size in an *in vivo* model of neonatal HIE in rats. Utilizing Oxygen-Glucose-Deprivation (OGD) as an *in vitro* model of cerebral ischemia, we demonstrate that inactivation of the EP1-receptor as well as activation of the EP4-receptor is protective in two cell types involved in HIE induced brain injury: neurons and endothelial cells. We show that amelioration of cell death by EP4-receptor stimulation is at least partially dependent on PKA activity. Also, activation of the EP4-receptor causes nuclear translocation of β-catenin, a transcriptional coactivator of Tcf/Lef-regulated genes. Inhibition of PKA partially abolishes EP4 induced nuclear translocation of β-catenin, suggesting a potential PKA/β-catenin signalling mechanism downstream of the EP4-receptor that might be involved in neuroprotection after hypoxic-ischemia.

We also show that the anti-ulcer drug and EP2-4 agonist misoprostol is protective in endothelial cells after OGD, primarily through activation of the EP2 and EP4 receptors.

The current study shows that specific inactivation of the EP1-receptor and activation of the EP4-receptor protects the neonatal brain from HIE, probably a protective effect on neurons as well as on endothelial cells. We also provide evidence that EP4-receptor downstream signalling in neurons acts via a PKA/β-catenin dependent mechanism.

Therefore, this work will shed some light on prostaglandin receptor signalling in neurons and endothelial cells in a model of cerebral ischemia and provide evidence for potential targets of pharmacological treatment to ameliorate infarct size in neonatal HIE.