Platelets play a central role in the development of the arterial thrombosis in heart disease. They respond to a variety of extracellular stimuli to undergo a rapid aggregation response, releasing active granule contents and leading to a rapidly growing thrombus. Central amongst these agonists are thromboxane A$_2$ and ADP which operate through G protein-coupled receptors (GPCRs) on the platelet surface: TP$_\alpha$ and TP$_\beta$ for thromboxane A$_2$ and P2Y$_1$ and P2Y$_{12}$ for ADP. Two of the major therapeutic approaches in the treatment of arterial thrombosis, aspirin and clopidogrel, target platelet receptors for these two major activatory agonists, with aspirin treatment reducing TP receptor signalling and clopidogrel blocking P2Y$_{12}$ receptor activation. Unfortunately a significant number of patients (~30%) display a degree of resistance (i.e. they suffer a thrombotic event) to either therapy. A recent study from our laboratory revealed cross-desensitization between ADP and thromboxane receptor signaling in human platelets (Barton et al., 2008). In this study we sought to investigate if pretreatment of human platelets with either aspirin or clopidogrel, which will reduce TP and P2Y$_{12}$ responsiveness respectively could also alter the sensitivity of other receptor systems.

All experiments were undertaken in platelets taken from volunteers as previously described (Barton et al., 2008). Receptor and platelet function was assessed in volunteers before and after drug administration by light transmission aggregometry as previously described.

In an initial patient study we discovered that there was increased platelet aggregation in response to a maximal concentration of the TP receptor agonist U46619 (10 $\mu$M) following patient treatment with clopidogrel. Further studies revealed that in patient's resistant to clopidogrel treatment (n=2) there was no significant change in TP receptor function. Importantly in patients with effective P2Y$_{12}$ blockade a number (2 out of 5) did display a significant increase in TP receptor responsiveness. In a parallel study we investigated if P2Y receptor responsiveness was altered in patients administered aspirin. Importantly we discovered that ADP-stimulated P2Y platelet receptor function was increased (10-20%) in patients following aspirin treatment. In both of these studies patient numbers were too low to place any statistical significance to our findings.

In conclusion, although preliminary our results suggest that blockade of TP receptor responsiveness in human platelets can increase P2Y signalling whilst P2Y$_{12}$ purinoceptor blockade increases TP receptor responsiveness. Such changes in receptor activity have potentially significant implications for the therapeutic use of aspirin and clopidogrel. For example is aspirin resistance due in part to increased P2Y purinoceptor signalling producing platelets hyper-responsive to ADP? Further work is ongoing to demonstrate the significance of our observations and to define the molecular mechanisms underlying these phenomena.

References: