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Evidence that Diclofenac and Celecoxib are Thyroid Hormone Receptor Beta Antagonists; use of in silico, Molecular and Pharmacological Techniques

Long term use of NSAIDs is linked to several detrimental side effects, inducing gastric bleeding and myocardial infarction. In order to understand the mechanisms by which NSAIDs induce detrimental effects in patients, many have studied the direct activity of NSAIDs on COX enzymes and developed novel models to explain the phenomenon. Since it is common for drugs to bind to multiple proteins, we used computational chemistry methods to investigate the potential for NSAIDs diclofenac and celecoxib to bind to nuclear receptors.

In silico screening predicted that both diclofenac and celecoxib could bind to a number of different nuclear receptors. We have chosen to investigate if the thyroid hormone receptor beta (TRβ) could be one of the novel targets for these NSAIDs. Results from TRβ luciferase reporter assays confirmed that both NSAIDs lack agonist activity, although display TRβ antagonistic properties; diclofenac IC50 $6.3x10^{-5}$ M and celecoxib IC50 $4.9x10^{-6}$ M. In order to determine the effects of NSAIDs in whole organ in vitro, we used isometric wire myography to measure the changes to triidothyronine (T3) induced vasodilation of rat mesenteric arteries. Male Wistar rats (350-450g) were killed by CO_2 asphyxiation in accordance with the UK Home Office regulations. Mesenteric arteries were dissected in Kreb's solution and incubated in the presence of the TRβ antagonist MLS000389544 (10^{-5} M), as well as diclofenac (10^{-5} M) and celecoxib (10^{-5}M). Results from myography showed a significant inhibition of T3 induced vasodilation compared to controls (Figure 1).

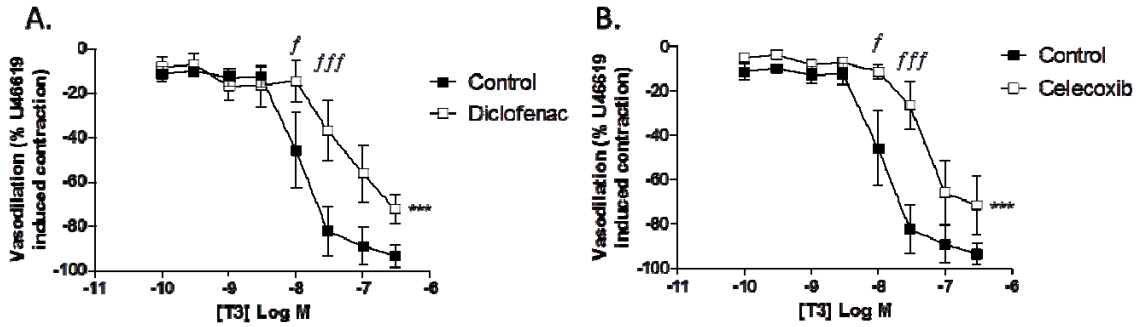

Figure 1. L-Triiodothyronine (T3) induced vasodilation in mesenteric arteries pre-contracted with EC_{80} U46619 ($3x10^{-7}$M). T3 vasodilation in the presence of A. 10^{-5}M Diclofenac and B. 10^{-5}M celecoxib. Data is presented as mean ± SEM of an n=6, and significance is represented as *** p=<0.001 by two way ANOVA and *f* =p<0.05 and *fff* =p<0.001 by Bonferroni post hoc test.

These results highlight the benefits of computational chemistry methods used to retrospectively analyse well known drugs for side effects. Using *in silico* and *in vitro* methods we have shown that both celecoxib and diclofenac exhibit off-target TRβ antagonist behaviour, which may be linked to their detrimental side effects.