Can NSAIDs alter thyroid hormone function?

Non-steroidal anti-inflammatory drugs (NSAIDs) are taken to treat pain and inflammation, and are the most frequently taken over the counter drug type taken worldwide. They work by inhibiting cyclooxygenase (COX) enzymes, whose products are used by other enzymes to biosynthesise a range of prostanoids. However, the NSAIDs also inhibit COX1, a key enzyme that is present in all cells in the body. Inhibition of COX1 leads to one of the major side effects of NSAIDs, gastric bleeding, and for this reason new COX-1 sparing drugs were created such as celecoxib. For people having to take NSAIDs on a daily basis this was an important development, but unfortunately these drugs were later found to have cardiovascular complications, furthermore, the chances of having a myocardial infarction following other NSAIDs such as diclofenac were also found to be increased. Much research followed to find out whether the cardiovascular side effects were due to the inhibition of COX1 or COX2. While on-target effects of NSAIDs are the likely to be the major cause of side effects, we investigated whether NSAIDs could also have off-target effects.

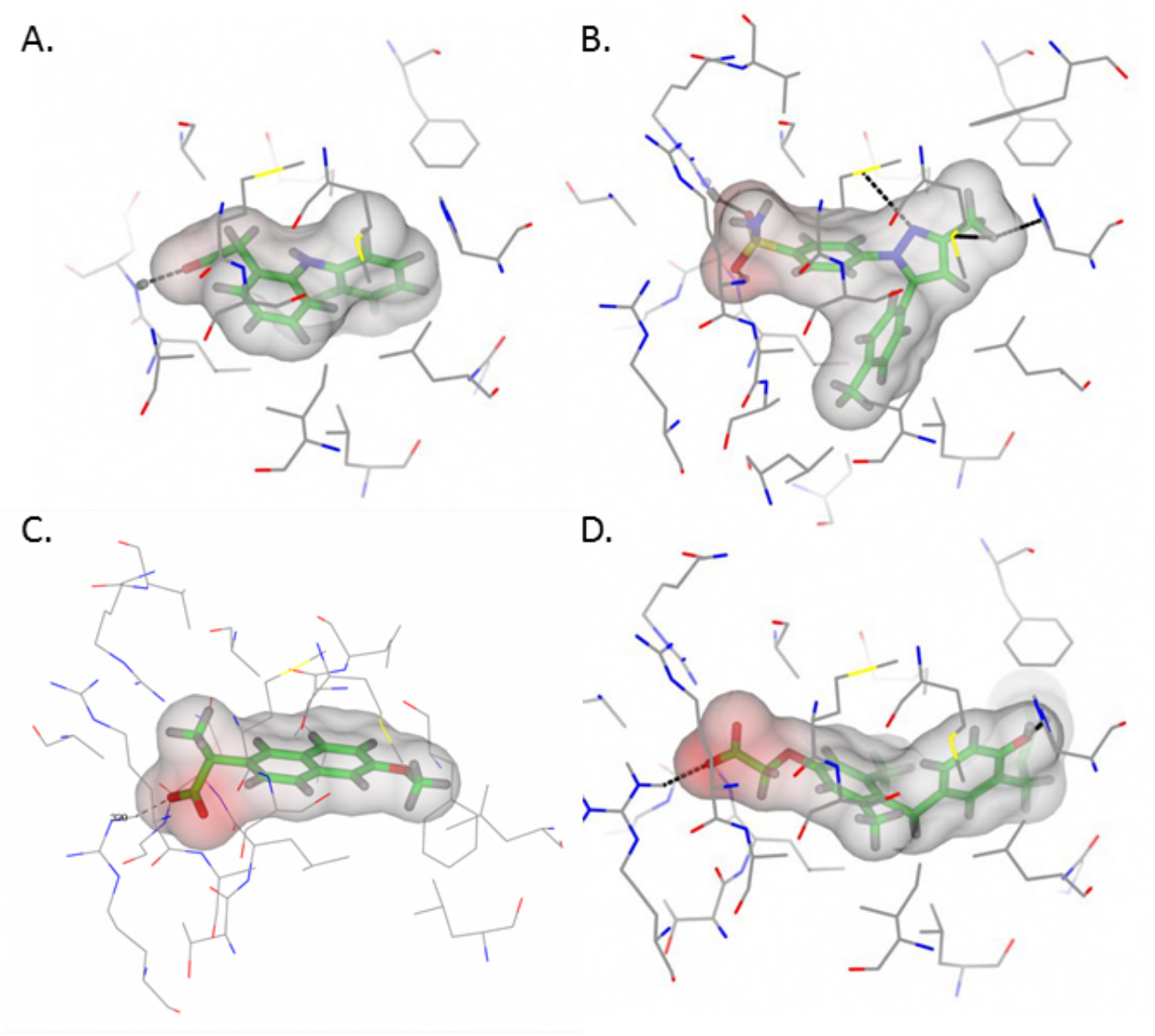

Fig. 1. Docking analysis using three TR? crystal structure with three different ligands; A. diclofenac; B. celecoxib; C. naproxen and D. original ligand present in 1Q4X. Surface shows active site of PDB 1Q4X entry; ligands are represented by ball-and-stick, side-chain residues of TR? are represented by cylinders. Dashed lines represent hydrogen bond interactions to amino acid residues in TR?. Transparent surfaces are coloured by electrostatic charges. Side-chain residues shown are within 4 Å of bound ligand

Using computational chemistry methods, we took the structures of diclofenac, celecoxib and naproxen and investigated whether they could theoretically bind to important nuclear receptors. We chose diclofenac since it binds to both COX1 and COX2, whereas celecoxib is specific for COX2; both of these have cardiovascular side effects. We used naproxen since it can bind to both COX1

and COX2 and is considered relatively cardio-sparing (i.e. safer than the other two drugs). Nuclear receptors are of interest, since they have long term impact on how cells function, and small changes in the way in which these receptors signal lead to really big functional changes in the whole body.

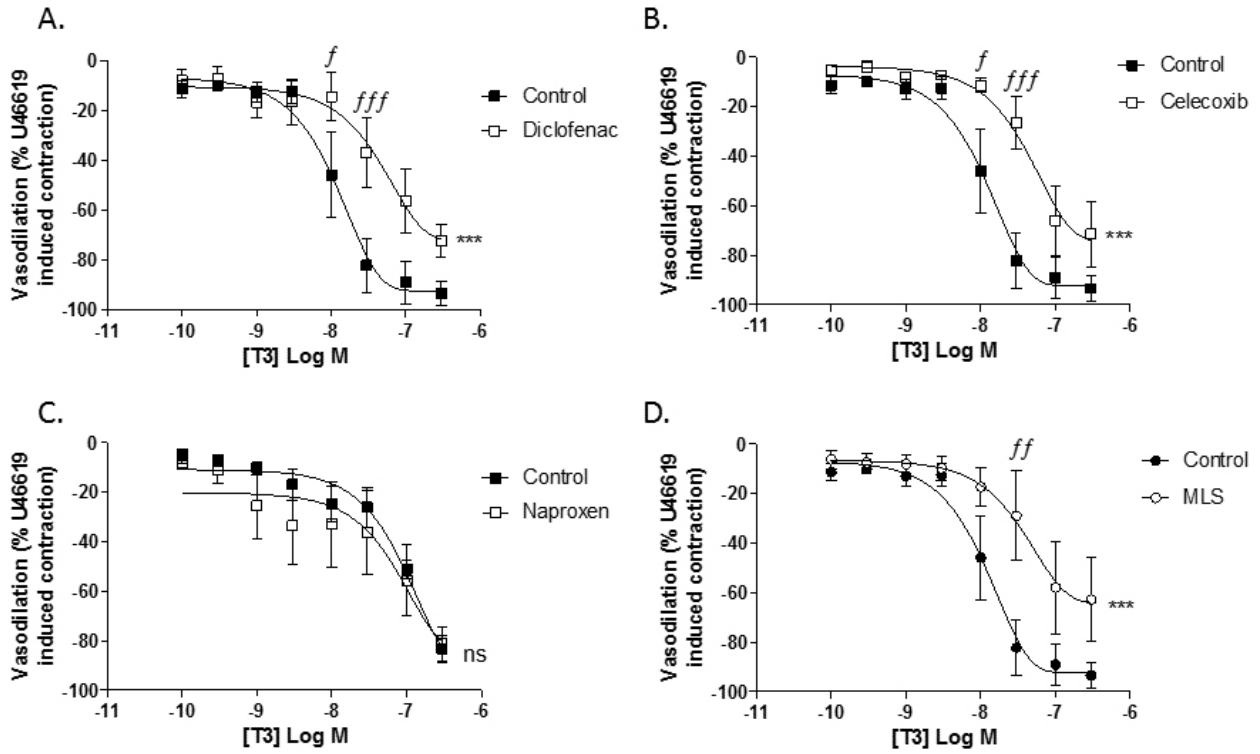

Fig. 2. L-Triiodothyronine (T3) induced vasodilation in the presence of NSAIDs. Arteries were incubated with A. 10?5Mdiclofenac, B. 10?5Mcelecoxib, C. 10?5Mnaproxen and D. 10?5M MLS (thyroid hormone receptor antagonist); following 30min arteries were pre-contracted with EC80 U46619 (3 × 10?7 M) and dilation to T3 determined. Data is presented as mean ±SEM, and significance is represented as ***p= b0.001 by two way ANOVA and significance compared to control at each concentration by Bonferroni post hoc test f=p

We found that diclofenac and celecoxib could, in theory, bind to thyroid hormone receptors, and then using other methods we found that these drugs would prevent thyroid hormone receptors from being bound by and activated by thyroid hormones. Therefore, in theory at least, thyroid hormones would still be produced, but they would no longer be able to signal correctly. We checked this result using arteries, and showed that thyroid hormones (T3) can cause dilation, and that addition of diclofenac and celecoxib, but not naproxen could prevent T3 from inducing dilation. The concentrations that we used in the experiment are difficult to translate into real life situations, but the evidence we have so far suggests that the diclofenac and celecoxib's side effects might be in

part attributed to an interaction with the thyroid hormone signalling which could contribute to the cardiovascular side effects. This helps us to understand what chemical structures are needed to create a drug that can be taken for pain relief and to decrease inflammation without the terrible side effects.

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Publication

Evidence that diclofenac and celecoxib are thyroid hormone receptor beta antagonists.
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