Next generation of paracetamol-related analgesics

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Background: Paracetamol possesses a unique pharmacological profile and is one of the most consumed drugs worldwide. However it needs to be administered at high doses and an extensive intake cause severe liver necrosis. Further development of paracetamol has been limited as its analgesic mechanism is not completely elucidated. Recently a new conceptual framework was unveiled which postulates that paracetamol acts as a prodrug and experience Fatty Acid Amide Hydrolase (FAAH)-mediated biotransformation into a potent Transient Receptor Potential Vanilloid 1 (TRPV1) activator AM404 (N-arachidonoyl phenolamine). AM404 acts on supraspinal neurons in the brain and mediates paracetamols anti-nociceptive effects in rodents (1). Our aim is to utilize computational insights to design new non-liver toxic paracetamol analogues with increased efficacy towards TRPV1-mediated anti-nociceptive systems.

Methods: Computational chemistry was applied to investigate the compatibly of compounds towards both FAAH and TRPV1 followed by functional testing towards target proteins. The anti-nociceptive properties of selected candidates were evaluated in several animal models as well as their ability to induce liver injury.

Results: We have been able to develop several anti-nociceptive candidates. Some substances displays more efficient interactions with target proteins than the paracetamol metabolite 4-aminophenol. This includes 4-hydroxy-3-methoxybenzylamine (HMBA) and its corresponding conjugate arvanil (pEC50=9.7+/-.01) which is approximately 150 times more potent than AM404 (pEC50=7.5+/-.01). Further evaluation showed that HMBAs anti-nociceptive actions were dependent on functional FAAH and TRPV1. Furthermore no liver injury was detected when evaluating clinical relevant biomarkers including liver histology.

Conclusion: We conclude that simultaneous consideration of both FAAH and TRPV1 in silico is an effective strategy to develop new analgesic compounds possessing a paracetamol-like pharmacology and concurrently evading apparent liver toxic effects. By utilizing and optimizing the anti-nociceptive mechanism of an existing drug this approach reduce the risks of translational issues. However future clinical trials has to be performed to validate and evaluate their clinical efficacy.

(1) Hogestatt E.D. et al. (2005).