Untargeted metabolomics highlight the potential antidepressant activity of a novel adenosine receptor antagonist

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Background: Depression is recognized as one of the main contributors to the worldwide burden of disease and is truly the illness of our times. It was estimated in 2017 that approximately 4.4% of the global population was affected by depression. The ongoing pandemic we find ourselves in has only served to exacerbate this burden, with an estimated average increase of 27.6% in global depression cases. Fortunately, many treatments for depression do exist, ranging from psychosocial interventions to antidepressant medications. However, existing treatments are not always effective or have varying degrees of success between individuals. Thus, there is a need to research alternative therapies, such as adenosine receptor (AR) antagonists (focusing on the antagonists of the A1 and A2A receptor subtypes). AR antagonists have attracted much attention as potential drug targets for various illnesses and represent a possible new class of antidepressants. One likely candidate to be investigated is 2-(3,4-dihydroxybenzylidene)-4-methoxy-2,3-dihydro-1H-inden-1-one (test compound), a recently synthesized novel AR antagonist exhibiting dual A1 and A2A AR affinity in the low micromolar range. This pilot study evaluates the test compound's potential as an antidepressant by comparing the metabolic profiles of rodents treated with the test compound to known antidepressants and vehicle control by means of untargeted metabolomics.

Methods: A vehicle control group and two reference compounds, namely KW-6002 (a commercially available AR antagonist showing antidepressant capabilities) and imipramine (a tricyclic antidepressant), were included alongside the test compound. Brain tissue was acquired from an ***in vivo*** study where male Sprague Dawley rats were either untreated or treated with test or reference compounds and subjected to the forced swim test. Metabolites were subsequently extracted from the acquired brain tissue and analyzed via untargeted 1H- NMR and GC-MS/MS techniques**.**

Results: Interestingly, the test and reference compounds induced similar metabolic changes. The concentration of several cerebral organic- and fatty acids was significantly lower in all the AR-antagonist-treated rats when compared to the vehicle control, which highlighted a perturbed fatty acid metabolism in the brain of the treated rodents. Abnormalities in fatty acid metabolism have been documented in depressed patients, and however, the involvement of fatty acid metabolism in antidepressant activity needs to be clarified.

Conclusion: The test and reference compounds exhibited similar metabolic profiles, indicating that the test compound may possess antidepressant capabilities.

Keywords: Antidepressant; Depression; Untargeted Metabolomics; Adenosine Receptor Antagonist; Fatty Acid Metabolism; Metabolic Profile.