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Azidobupramine, a novel chemical tool to enlighten antidepressants mode of action

Svenja Nina Reinders[1], Thomas Kirmeier[2], Ranganath Gopalakrishnan[2,3], Vanessa Ganal[2], Anna M Werner[2], Serena Cuboni[2], Georg C Rudolf[2,5], Stephan A Sieber[3], Florian Holsboer[1], Theo Rein[2] and Felix Hausch[2]

[1]Max Planck Institute of Psychiatry, Germany
[2]Ecole Polytechnique Federale de Lausanne, Switzerland
[3]Technical University Munich, Germany
[4]Bayer House, India

Antidepressants were discovered in the 1950s but their underlying molecular mechanisms are still incompletely understood. Revealing the identity of additional targets may contribute to a better understanding of the antidepressants` mode of action. The aim of this study was to develop a chemically modified antidepressant enabling the identification of alternative direct drug targets. For this purpose, azidobupramine, a structurally related analogue of imipramine, was synthesized featuring two additional chemical groups, one for photoaffinity labeling (PAL) and the other for copper(I) catalyzed azide alkyne cycloaddition (CuAAC). Using the serotonin transporter as model target, we demonstrate that azidobupramine is characterized by equilibrium dissociation constants (Ki) equivalent to those of clinically active substances. Furthermore, we show that azidobupramine forms chemical bonds with the transporter after UV light exposure in living cells. Thus, azidobupramine represents a promising and versatile tool for the discovery of novel direct antidepressant target sites in living systems.

svenja_reinders@psych.mpg.de

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