Ruprecht-Karls-Universität Heidelberg
Medizinische Fakultät Mannheim
Dissertations-Kurzfassung

Investigation of the neurovascular coupling of $D_{2/3}$ dopamine receptor availability in humans using simultaneous PET/MR. A methodology for studying dopamine supersensitivity

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International guidelines recommend maintenance treatment with antipsychotic agents as the primary therapeutic regime following the initial episode of schizophrenia. Nevertheless, prolonged treatment with dopamine antagonists has been linked to a heightened risk of relapse upon discontinuation and the development of treatment resistance. One potential underlying molecular mechanism could be dopamine supersensitivity, characterized by alterations in the functional domain of the dopamine system, leading to an increase in dopamine receptor density and heightened sensitivity of the dopaminergic system to dopamine agonists. Neurovascular coupling, the link between synaptic properties like dopamine $D_{2/3}$ receptor availability and the hemodynamic effects of dopamine signaling, has been examined in translational models utilizing functional magnetic resonance imaging (fMRI) alongside various dopamine antagonist interventions. While there exists compelling evidence for the neurovascular coupling of dopamine $D_{2/3}$ receptors in animal models, significant knowledge gaps remain regarding the dynamic interplay between dopamine neurochemistry and hemodynamic dopamine responsiveness in humans.

This study aims to assess the hemodynamic alterations induced by the dopamine agonist apomorphine as a pharmacological challenge for the first time in humans, and to correlate these functional changes with the baseline non-displaceable binding potential of dopamine $D_{2/3}$ receptors. [^{18}F]fallypride positron emission tomography (PET) imaging was used to quantify dopamine $D_{2/3}$ receptor availability in nine healthy subjects. Perfusion was measured both at baseline and following administration of the dopamine agonist apomorphine using simultaneous perfusion-weighted fMRI.

The acute administration of the dopamine agonist led to acute changes in perfusion within the caudate nucleus of healthy volunteers. These individual apomorphine-induced alterations in perfusion within the caudate nucleus and striatum exhibited a negative correlation with baseline [^{18}F]fallypride non-displaceable binding potential.

This study introduces a novel methodology for investigating neurovascular coupling of the dopamine system in humans based on simultaneous PET/MR-imaging. It presents a unique paradigm for evaluating dopamine sensitivity, thereby facilitating the exploration of the dopamine supersensitivity hypothesis.