

RESEARCH HIGHLIGHT

Hallucinogens induce a specific barcode of phosphorylation on the serotonin_{2A} receptor that underlies a weaker receptor desensitization and internalization

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The serotonin (5-Hydroxytryptamine, 5-HT)_{2A} receptor represents one of the most striking examples where functional selectivity (or ligand-biased signaling) is transduced in distinct behaviours^[1]. This receptor is the main target of psychedelic hallucinogens such as mescaline, lysergic acid diethylamine and psilocybin, which reproduce some core symptoms of schizophrenia and are often used to probe the disease. Why some 5-HT_{2A} receptor agonists exhibit hallucinogenic activity, whereas structurally closed ligands with comparable affinity and agonist activity (e.g. ergotamine and lisuride) lack such a psychoactive activity remains an incompletely resolved paradox^[1-3]. In a recent paper published in *Molecular and Cellular Proteomics* (doi: 10.1074/mcp.M113.036558), we demonstrated a biased phosphorylation of the 5-HT_{2A} receptor in response to hallucinogenic versus non-hallucinogenic agonists.

Keywords: Serotonin; 5-HT_{2A} receptor; hallucinogen; functional selectivity; phosphoproteomics

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Using high-resolution mass spectrometry to map the phosphorylation sites on the 5-HT_{2A} receptor, we discovered two clusters of phosphorylation sites triggered by agonists and located in the third intracellular loop of the receptor. Interestingly, one cluster (Ser²⁸⁰, Ser²⁸⁷, Ser²⁸⁸, Ser²⁹⁰ and Ser²⁹¹) specifically appeared in cells treated with hallucinogens but not when they are exposed to non-hallucinogenic agonists. Mass spectrometry data indicated

that specific phosphorylation of Ser²⁸⁰ upon hallucinogen treatment is a necessary step leading to the phosphorylation of the other residues of this cluster. A new phosphorylation site-specific antibody confirmed the biased phosphorylation of Ser²⁸⁰ in the mouse prefrontal cortex. Finally, site mutagenesis of Ser²⁸⁰ revealed that its biased phosphorylation underlies the weaker desensitization and internalization of 5-HT_{2A} receptor

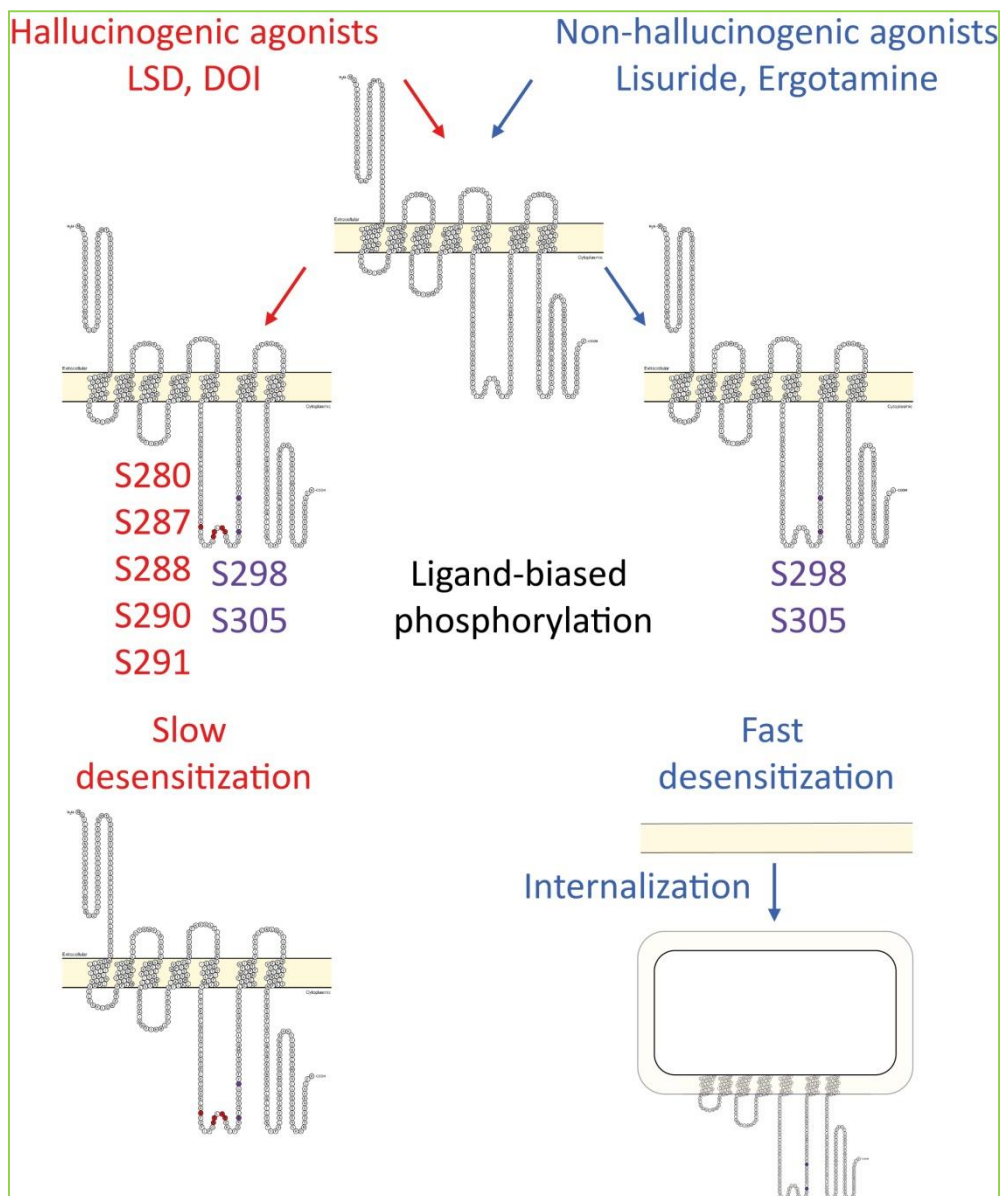


Figure 1. Summary figure describing the findings of the highlighted article. The 5-HT_{2A} receptor is differentially phosphorylated when stimulated with hallucinogenic agonists (DOI or LSD) versus non-hallucinogenic agonists (Lisuride or ergotamine). Whereas the Ser298 and the Ser305 phosphorylation is triggered by the two categories of agonists, the phosphorylation of the Ser280 is specifically induced by hallucinogens and not by non-hallucinogenic agonists. Ser280 is the priming site leading to the phosphorylation of a larger cluster of phosphorylation sites located in the third intracellular loop of the 5-HT_{2A} receptor. Phosphorylation of the Ser280 leads to a prolonged sensitization of the receptor when stimulated with hallucinogenic agonists versus non-hallucinogenic agonists.

elicited hallucinogens, compared with non-hallucinogenic agonists.

G protein-coupled receptor (GPCR) phosphorylation elicited mainly, but not exclusively, by G protein-coupled receptor kinases (GRKs) is the initial event triggering the recruitment of beta-arrestins, the internalization of the receptor and the engagement of beta-arrestin-dependent

signaling pathways [4]. Very recently, specific patterns of phosphorylation of some GPCRs following their stimulation have been described with variations reflecting genetic polymorphism (beta 2 adrenergic receptor) [5], partial vs. full agonism (μ -type opioid receptor) [6], biased agonism (beta 2 adrenergic receptor) [7] or homo/heterodimerization (opioid receptors) [8]. This phosphorylation barcode is emerging as a general

mechanism that correlates with specific modifications of signaling or desensitization of GPCRs [9]. The biased phosphorylation of the 5-HT_{2A} receptor we describe in our work [10] represents a new example of how two categories of full agonists of a given GPCR generate subtle differences in the phosphorylation patterns of the receptor that might underlie their distinct ability to trigger psychoactive-like effects.

Conflict of interest

The authors declare that they have no conflict of interest.

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