Acute and Withdrawal Effects of 4-EA-NBOMe on Basal Synaptic Transmission in Rodent and Human Neuronal Models

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New psychoactive substances (NPSs) are synthetic or modified compounds developed to replicate the effects of controlled drugs while evading existing legal restrictions on their production, distribution, and use. Despite their growing availability, the toxicological profiles and pharmacological properties of many NPSs remain insufficiently characterized. Among the prominent classes of these substances are the N-2-methoxybenzyl derivatives (NBOMes), initially synthesized as potent 5-HT_2A receptor agonists with pronounced psychedelic effects. NBOMe compounds have been linked to severe adverse outcomes, including agitation, tachycardia, hypertension, seizures, and, in cases of overdose, death. One such compound, 4-ethylamphetamine-NBOMe (4-EA-NBOMe), structurally similar to amphetamine, was first identified in Germany in 2014. Owing to the involvement of its ethyl side chain in metabolic reactions, 4-EA-NBOMe engages a wider range of biochemical pathways compared with structurally related analogues. Recent findings indicate that 4-EA-NBOMe alters the excitability of primary cortical neurons and modulates spontaneous excitatory postsynaptic activity, underscoring its potential for significant neurophysiological effects. Furthermore, several NBOMe analogues have been shown to increase dopamine availability within mesolimbic addiction pathways of the central nervous system, linking their neurocognitive effects to alterations in basal synaptic transmission beyond their primary actions on the serotonergic system. A detailed understanding of how 4-EA-NBOMe influences vesicular dynamics and the molecular machinery of synaptic transmission is therefore critical for mitigating the detrimental effects associated with NBOMe consumption. In this study, we investigate the effect of the acute expsoure and subsequent withdrawal from 4-EA-NBOMe on basal synaptic transmission in the major central nervous system synapses, using a combination of in vitro (primary neurons and organoid systems) and ex vivo (brain samples) rodent and induced-human neuronal samples. Through the use of electrophysiological methods, precise imaging and tracking method, and pharmacological manipulation, we aim to isolate and quantify the release and transmission dynamics of the principal neurotransmitter pathways, including glutamatergic, GABAergic, and dopaminergic signalling.