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The Bidirectional Effect of 2-AG on Hyperdopaminergic States: Implications for Therapeutic 2-AG Modulation in Psychosis

Catharine Mielnik,[1] Claudia Lutelmowski,[2] Julia Zebarth,[2] Junchao Tong,[3] Anna Pees,[3] Andrea Narvaez,[3] Kristyn Fournier,[3] Marija Milenkovic,[2] Wendy Horsfall,[2] Steven H. Liang,[4] Isabelle Boileau,[3] Walter Swardfager,[2] Heather B. Bradshaw,[5] Neil Vasdev,[3] Ali Salahpour,[2] and Ruth A. Ross[2]

[1]Univ of Toronto; [2]University of Toronto; [3]Centre For Addiction and Mental Health; [4]Emory University; and [5]Indiana University Bloomington

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Background: Several conditions, including schizophrenia (SCZ), are believed to be related to dysregulation in dopamine (DA) signalling. Furthermore, the endocannabinoid system (ECS) is suggested to be dysregulated in DA pathologies: biosynthesis pathway of 2-arachidnoylglycerol (2-AG), a major endocannabinoid neurotransmitter, shown to be altered in SCZ; DAGL (2-AG synthesis) levels decreased; MAGL (primary 2-AG metabolism) expression levels significantly lower; elevated 2-AG observed. Despite mixed findings, elevation of 2-AG is coveted in certain contexts; clinical trials of MAGL inhibitors (MAGLi) currently underway for PTSD and Tourette syndrome. Evidence suggests that increasing 2-AG might be detrimental in hyperDA pathologies. It's imperative to understand MAGLi in vulnerable populations, and whether decreasing 2-AG is therapeutic. Therefore, we assessed preclinical effects of modulating 2-AG in two models of hyperDA; based on well-established associations between psychopathologies and increased subcortical dopamine.

Methods: Genetic (adult DAT-knockout (DATKO) and pharmacological (C57Bl/6J with amphetamine) models of hyperDA were treated acutely with a MAGLi (MJN110, 5mg/kg) or DAGLi (DO34, 30mg/kg), and tested on several behavioural assays. Lipidomic and molecular analyses were completed (striatal brain samples), and partial correlation networks were generated. Using the novel positron emission tomography (PET) radiotracer for MAGL, [^{18}F]MAGL-2102, and an established radiotracer for imaging the cannabinoid receptor type-1 (CB1), [^{18}F]FMPEP-d_2, we interrogated the status of MAGL and CB1 *in vivo* in hyperDA states, comparing DATKO vs WT littermate controls. Data analyzed using three-way ANOVA (behaviour), Student's t-test (lipidomics), and repeated measures ANOVA for PET quantification (with appropriate post hoc analyses for all tests).

Results: DATKO show exploratory hyperactivity, impaired sensorimotor gating, blunted response to psychostimulants, and disrupted lipid profiles. Brain uptake of [^{18}F]MAGL-2102 (male $>$ female) was similarly and significantly decreased in both sexes in DATKO (whole brain AUC: -21% and -17% in female and male DATKO, respectively). [^{18}F]FMPEP-d2 (CB1), on the other hand, showed the opposite sex-dependent binding in WT (female $>$ male), with a sex-dependent significant decrease in tracer uptake in female DATKO (-27% in whole brain AUC), but not males (-11%, non-significant). When treated with a MAGLi, DATKO showed exacerbation of hyperlocomotion, sensorimotor deficits, and further disruption of lipid networks. MAGLi increased reward association in DATKO, but not WT, suggesting an addiction liability in certain populations. MAGLi effects weren't limited to DATKO; it exacerbated psychostimulant responses in C57BL/6J. Data suggests that increasing 2-AG via MAGLi exacerbates states of hyperdopaminergia, mediated by CB1. Interestingly, decreasing 2-AG synthesis (via DAGLi) presented opposite effects on all measured hyperdopaminergic behavioural outputs in both DATKO and C57BL/6J.

Conclusion: Present study demonstrates profound brain-region specific remodelling of 2-AG in hyperDA states. The work highlights hitherto unrecognized potential for detrimental effects of MAGLi in certain disease states. It also revealed a potential therapeutic for hyperDA pathologies by reducing 2-AG synthesis via DAGLi.