Exploring the time and concentration dependence of psychedelic exposure to neuronal cultures using a high-density microelectrode array system

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INTRODUCTION

Functional imaging and neurophysiology technologies have provided a clinical link to neuroplasticity mechanisms of psychedelics[1,2]. Since neuroplasticity changes are similar between humans and animals after psychedelic exposure[3], assessment of neuronal firing patterns in rodent cell cultures could increase throughput when investigating mechanisms of novel psychedelic compounds.

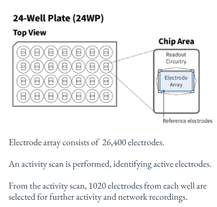
As an exemplar tool molecule, we assessed the time and concentration dependence of 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) to see the potential sensitivity of neuronal functional dynamics after psychedelic exposure in cell cultures using a high-density microelectrode array (MEA) system. 5-MeO-DMT has recently completed a Ph1 and Ph2a open label study with early evidence of potential durable signals in treatment resistant depression[4,5].

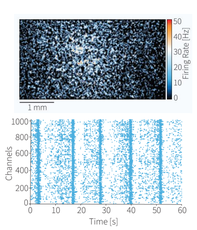
MATERIALS & METHODS

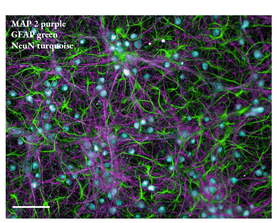
Cell culture & compound addition:
Cortical preparations from E17.5 rat embryos (Wistar Han) were seeded on PDL and laminin coated MaxTwo 24-well MEA plates with 26,400 electrodes/well (MaxWell Biosystems). At 14 DIV, cortical preparations were treated with 5-MeO-DMT or vehicle control (DMSO; 0.2 % in all wells).

High-density MEA:
Network scans were performed pre- compound addition and thereafter at 0.5, 1, 2, 3 and 24 hours post compound addition. Network analysis was performed with fixed settings for all timepoints. Activity data post compound addition was divided with pre-recordings to compensate for well-to-well variation.

MaxTwo High-Density Microelectrode Array System.



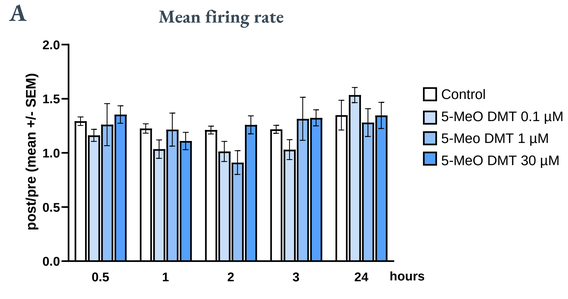


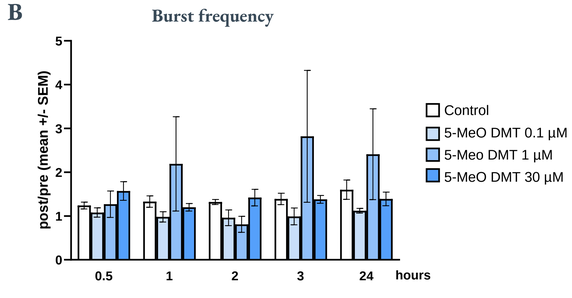


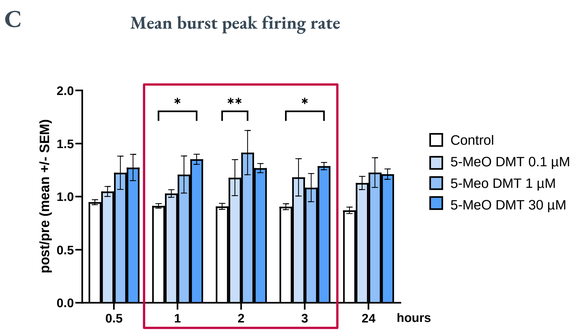
Immunocytochemistry; E17.5 rat cortex culture.
Acquired with a 20× wide field objective.

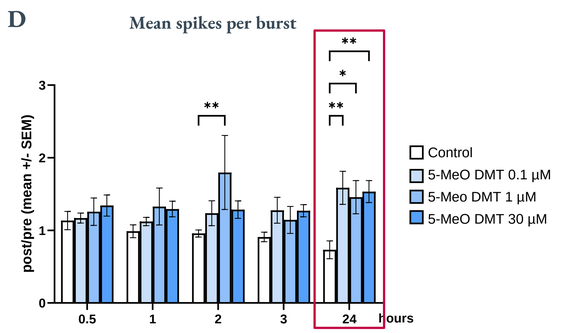
RESULTS

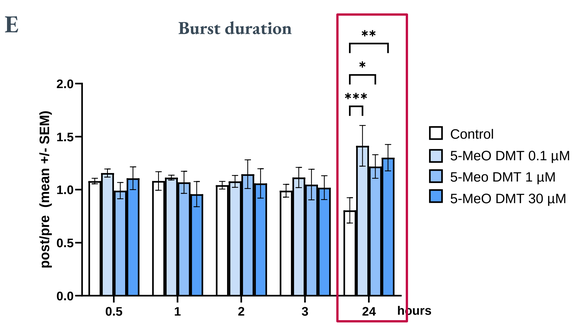
5-MeO-DMT increases network activity on MEA in a concentration and time dependent manner without affecting total mean firing rate or burst frequency





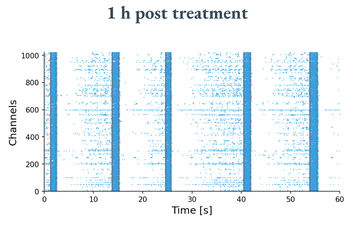


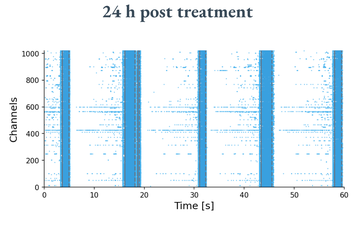




No difference in mean firing rate (A) or burst frequency (B) was observed between control cells and cells treated with 5-MeO-DMT. There was an acute (1-3 h), statistically evident concentration-dependent increase in mean burst peak firing rate (C) in cells treated with 5-MeO-DMT. This was intriguingly followed by a profound and statistically significant increase in mean spikes per burst at two and 24 hours post compound addition (D) as well as burst duration at 24 h (E) for all concentrations tested.
n=6 wells per condition. Two-way ANOVA with Dunnett's post hoc test.
* p<0.05, ** p<0.01, ***p<0.001.

Raw data example:
Raster plots from one well treated with 0.1 µM 5-MeO-DMT, 1 hour and 24 hours post-dosing, respectively.





CONCLUSIONS

Using the high-density MEA technique, we were able to detect psychedelic-induced changes in neuronal function in vitro. These initial findings suggest a dynamic and temporally regulated modulation of neuronal activity, with both acute and delayed effects on burst firing characteristics that may involve different molecular and cellular pathways involved in synaptic transmission, neuronal excitability, and network dynamics.

More in-depth assessments of 5-MeO-DMT mechanisms of action, coupled with a range of pharmacologically and qualitatively varied psychedelic drugs, may pinpoint common and diverse mechanisms of action of psychedelics and how they may link to the expression of diverse altered states of consciousness.

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