Pro-inflammatory cytokines induce anhedonia in mice and increase monoamine transporter activity in the nucleus accumbens

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Introduction

- Evidence points to a role of pro-inflammatory cytokines in the pathogenesis of major depressive disorder (MDD);
- Lipopolysaccharide (LPS) induces a rapid release of pro-inflammatory cytokines which leads to anhedonia, i.e. the inability to experience pleasure;
- How cytokines induce anhedonia is largely unknown.

Hypothesis: Peripheral cytokines reach the brain, increase monoamine transporter activity, leading to increased metabolism of monoamines and eventually anhedonia.

Material and methods

- **Intracranial self-stimulation (ICSS) -** An electrode was placed in the lateral hypothalamus of 8 male C57BL6/J mice. They were housed in groups and trained in the ICSS paradigm. ICSS thresholds and response latencies were measured daily.
- **Microdialysis -** A microdialysis probe was implanted in the nucleus accumbens of 30 male C57BL6/J mice. Microdialysis was performed in individually housed, conscious, freely moving mice. 30-minute samples were analyzed by HPLC.
- **Drugs -** Animals were i.p. injected with saline or 133 µg/kg LPS. The triple reuptake inhibitor (TRI) DOV 216,303 (5 mg/kg) was injected i.p. 30 minutes before the LPS injection.

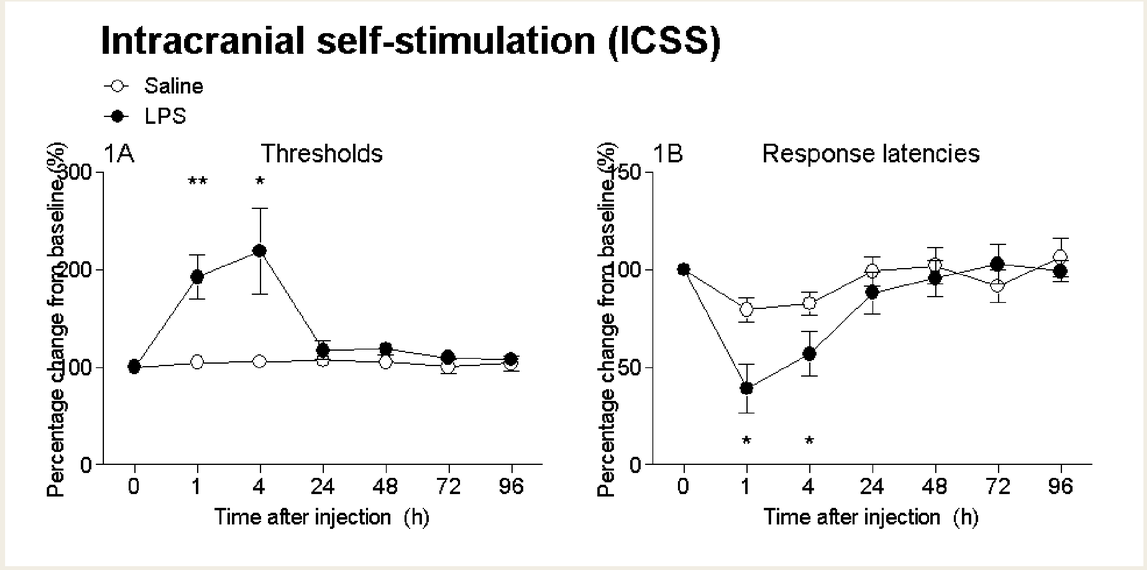

Figure 1: The effect of LPS on ICSS thresholds and ICSS response latencies. ICSS thresholds (A) and corresponding response latencies (B) were measured 1, 4, 24, 48, 72 and 96 h after exposure to LPS and are presented as mean percentage change from baseline values ± standard error of the mean. Statistically significant results are indicated as * $p < 0.05$ or ** $p < 0.01$.

Results

LPS induced anhedonia (Fig. 1A). Response latencies decreased significantly in LPS-exposed mice demonstrating that immobility did not affect the outcome of the ICSS study (Fig. 1B). Remarkably, LPS did not alter extracellular levels of dopamine (Fig. 2A) or serotonin (Fig. 2D), while their metabolites 5-HIAA (Fig. 2E), HVA (Fig. 2C) and DOPAC (Fig. 2B), were significantly elevated within 60 min after LPS administration. Pre-exposure to the triple re-uptake inhibitor DOV 216,303 abolished LPS induced increases in DOPAC and HVA, while 5-HIAA further increased. AUC values confirm that LPS-induced increases in monoamine metabolite levels are decreased by DOV 216,303 (Fig. 3F-3J).

Conclusions and hypothesis

- Cytokines induce anhedonia as reflected by increased ICSS thresholds;
- Cytokines increase formation of dopaminergic and serotonergic metabolites in the nucleus accumbens;
- Pre-exposure to the triple re-uptake inhibitor DOV 216,303 abolished LPS-induced increases in DOPAC and HVA, while 5-HIAA formation was only slightly inhibited.

We hypothesize that monoamine transporters play an important role in anhedonia, a core symptom of MDD.

Disclosure: There is no potential conflict of interest.

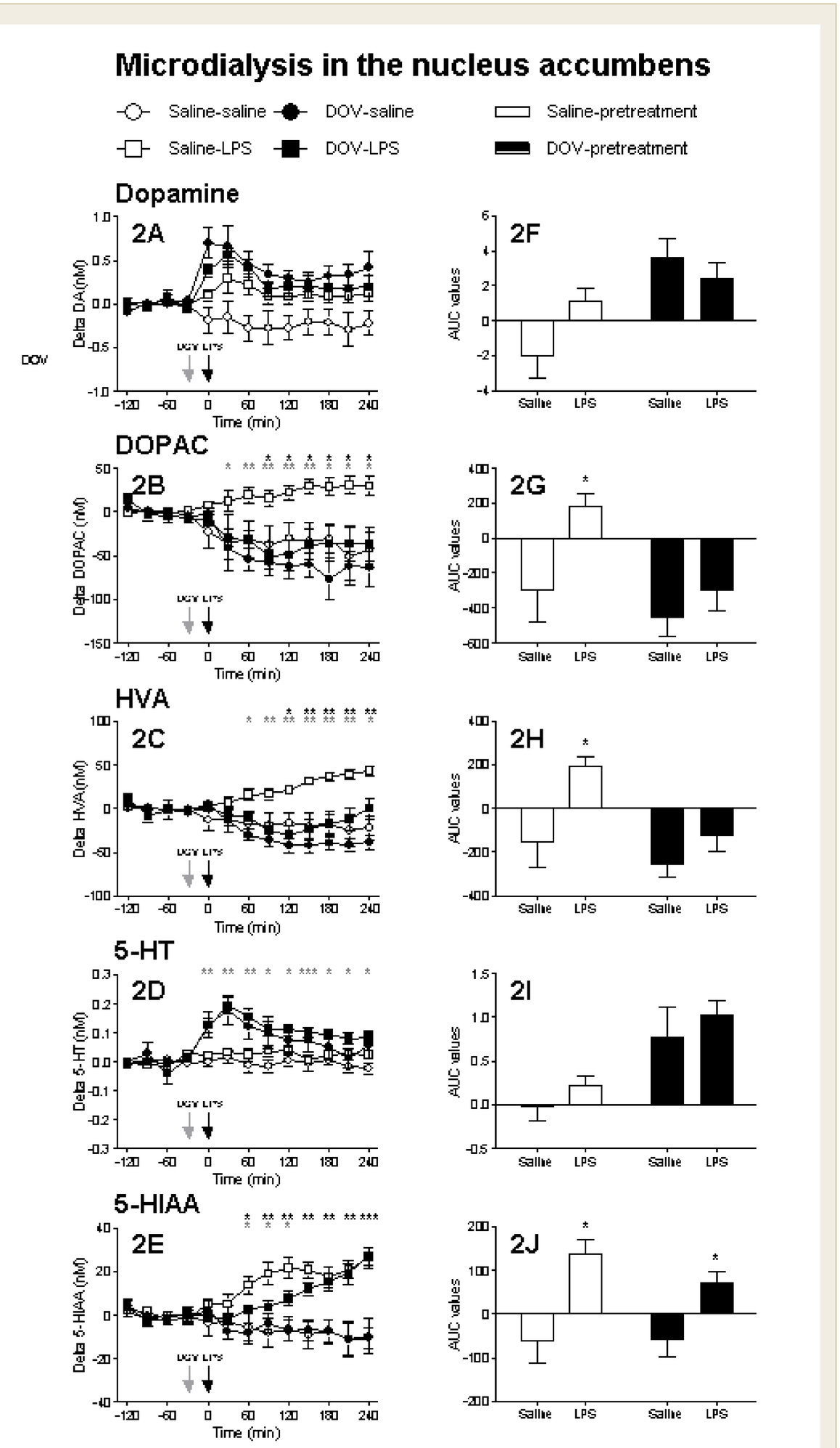

Figure 2: Microdialysis in the Nucleus accumbens. DA (A), DOPAC (B), HVA (C), 5-HT (D) and 5-HIAA (E) levels were measured under basal condition and after pre-exposure to saline (white symbols) or DOV 216,303 (black symbols) (time point -30 min) followed by a saline (bullets) or LPS injection (quadrangles) (time point 0 min). For each monoamine and monoamine metabolite the difference from baseline data (delta's) was presented as mean ± standard error of the mean (left column). Statistically significant results between saline-saline and saline-LPS treated mice at a single time point are indicated in black as * $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$. While statistically significant results between saline-LPS and DOV-LPS treated mice at single time points are indicated in grey as * $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$. Corresponding mean area under the curve (AUC) values ± standard error of the mean are shown in the right column (F-J). For AUC values, statistically significant differences between saline-saline and saline-LPS or DOV-saline and DOV-LPS mice are indicated as * $p < 0.05$.