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Lipopolysaccharide inhibits long-term potentiation and glutamate release in rat dentate gyrus

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Lipopolysaccharide (LPS), a component of gram-negative bacteria, activates microglia, resulting in the release of the proinflammatory cytokine interleukin-1 β (IL-1 β ; Schneider *et al.* 1998). IL-1 β inhibits long-term potentiation (LTP) in dentate gyrus *in vivo* (Murray & Lynch, 1998). We hypothesized that since LPS can trigger IL-1 β synthesis, it may mimic the effects of IL-1 β . In this study, the effect of LPS on LTP, glutamate release, expression of IL-1 β and the activity of c-Jun NH₂-terminal kinase (JNK), a stress-activated protein kinase, was assessed.

Male Wistar rats (300 g) were anaesthetized with urethane (1.5 g kg⁻¹ I.P.) and injected intraperitoneally with LPS (100 μ g kg⁻¹) or saline 3 h prior to tetanic stimulation. Electrophysiological recording from the dorsal cell body region of the dentate gyrus, in response to perforant path stimulation, commenced. Evoked EPSPs were similar in both groups. Following a 40 min post-tetanic recording period, rats were killed and the dentate gyri (untetanized and tetanized) were removed, sliced and frozen for later analysis. KCl-stimulated glutamate release (Whittaker *et al.* 1999) and IL-1 β (O'Donnell & Lynch, 1998) were assessed in synaptosomes prepared from untetanized and tetanized dentate gyri as previously described. The activity of JNK was analysed by western immunoblotting, followed by densitometric analysis (Whittaker *et al.* 1999).

The results show that LPS impairs LTP and reduces glutamate release in the dentate gyrus. LPS caused a significant increase in IL-1 β expression from 109.30 ± 40.1 to 377.9 ± 104.6 pg (mg protein)⁻¹ (means \pm S.E.M., $n = 5$, $P < 0.05$, Student's *t* test) and increased JNK activity from 65 ± 4.8 to 122.9 ± 18.36 arbitrary units (mean \pm S.E.M., $n = 3$, $P < 0.05$, *t* test).

The mean percentage increase in EPSP slope was 119.10 ± 2.17 % in saline and 100.81 ± 2.26 % with LPS ($n = 6$, $P < 0.01$, *t* test).

{ "Tableheading" on } [Table 1](#). Effect of LPS on glutamate release (μ mol mg⁻¹)

{ "Tableheading" off } Untetanized Tetanized

{ "#" on } Unstim Stim Unstim Stim

{ "#" off } Saline 0.613 ± 0.20 1.36 ± 0.33 0.76 ± 0.34 1.97 ± 0.44

LPS 0.720 ± 0.26 0.61 ± 0.33 0.45 ± 0.16 0.84 ± 0.12

* $P < 0.05$, Student's t test, mean \pm S.E.M., $n = 6$.

We propose that the LPS-induced impairment of LTP is due to an elevation in neuronal expression of IL-1 β , with a subsequent activation of JNK.

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