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TRANSPORT AND UTILIZATION OF ARGININE-CONTAINING PEPTIDES IN ALVEOLAR MACROPHAGES.

X. Yang[1], J.Y.C. Ma[2], J.K.H. Ma[1]
[1]West Virginia University: Morgantown, WV; [2]National Institute for Occupational Safety and Health: Morgantown, WV

Purpose. To investigate the transport system for small peptide uptake and the utilization of arginine-containing peptides for nitric oxide synthesis by lypopolysaccharide (LPS)-activated alveolar macrophages. **Methods.** The uptake of small peptides by rat alveolar macrophages (AMs) was studied using FITC-labeled (*) Arg-Lys*, Gly-Sar-Lys*, and β-Ala-Lys*. The kinetics of the peptide uptake in the presence and absence of Gly-Sar or Lys, were monitored by fluorometry. For NO production, AMs (10^6 cells/well) were incubated in Earle's medium with L-Arg or L-Arg-containing peptides (Arg-Lys, Arg-Gly, Arg-Gly-Asp) for 24 hr, with or without LPS (1 μg/ml) stimulation. Nitrite accumulation in the culture medium was determined as the indicator of NO production. The effects of transport systems on LPS-induced NO production were examined using Gly-Sar, L-Lys, 4-AMBA and LPC as transport inhibitors. **Results.** The FITC-derived small peptides were readily internalized by AMs with saturation at 3 hr. The uptake of Arg-Lys* and β-Ala-Lys* at concentration of 10 μM was blocked (70 - 80%) by Gly-Sar (200 μM) through competitive inhibition, but not by L-Lys, which shares a common cationic amino acid transporter with L-Arg. At concentration of 200 μM, the Arg-containing peptides were shown to be nearly equally efficient as L-Arg in providing substrate for NO production. These results suggested that the Arg peptides were internalized and subsequently hydrolyzed to yield L-Arg. The LPS-induced NO production was significantly attenuated by inhibitors of the transport systems. L-Lys, at 10 mM, inhibited NO production by about 40% when L-Arg was used as a substrate, while AMBA, at 0.5 mM, partially inhibited NO production (~ 20%) when the L-Arg-containing peptides were used as substrates. L-Lys, at 10 mM, also showed a partial inhibitory effect on the Arg peptide system. LPC at 1 mM, completely blocked the LPS-induced NO synthesis by AMs in either the L-Arg or the Arg peptide system. **Conclusions.** L-Arg-containing peptides can serve as a source to provide substrate for NO production. The uptake of these peptides by AMs may be mediated through an active peptide transport system similar to that of the pepT1 transporter. Our studies also showed that LPC is a potent inhibitor for the transport of small peptides in AMs.

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