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Leukotriene B₄ and lipoxin A₄ are regulatory signals for neural stem cell proliferation and differentiation

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Leukotrienes (LTs) and lipoxins (LXs) are lipid mediators that play a key role in regulating acute inflammatory responses. Their roles in neural stem cell (NSC) functions are of interest. We showed here that LTB₄ and LXA₄ regulated proliferation and differentiation of murine NSCs that were isolated from embryo brains. Proliferation of NSCs was stimulated by LTB₄ (3 to 100 nM) and blocked by receptor antagonist (IC₅₀=2.7 μM). In contrast, LXA₄ and its aspirin-triggered-15-epi-LXA₄ stable analog attenuated growth of NSCs at as little as 1 nM. Both lipoxygenase (LOX) inhibitors and LTB₄ receptor antagonists caused apoptosis and cell death. Gene chip analysis revealed that growth-related gene expressions such as epidermal growth factor (EGF) receptor, cyclin E, p27, and caspase 8 were tightly regulated by LTB₄; LXA₄ gave the opposite gene expressions. In addition to

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proliferation, LTB₄ induced differentiation of NSCs into neurons as monitored by neurite outgrowth and MAP2 expression. These results indicate for the first time that LTB₄ and LXA₄ directly regulate proliferation and differentiation of NSCs, suggesting these new pathways may be useful in restoring stem cells.—Wada, K., Arita, M., Nakajima, A., Katayama, K., Kudo, C., Kamisaki, Y., Serhan, C. N. Leukotriene B₄ and lipoxin A₄ are regulatory signals for neural stem cell proliferation and differentiation.

Key Words: inflammatory mediators • neural inflammation • BLT receptor • ALX receptors • neuron

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