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# Identification of a prostaglandin $D_2$ metabolite as a neuritogenesis enhancer targeting the TRPV1 ion channel

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Takahiro Shibata[1,2], Katsuhiro Takahashi[1], Yui Matsubara[1], Emi Inuzuka[1], Fumie Nakashima[1], Nobuaki Takahashi[3], Daisuke Kozai[3], Yasuo Mori[3] & Koji Uchida[1]

**Mast cells play important roles in allergic inflammation by secreting various mediators. In the present study, based on the finding that the medium conditioned by activated RBL-2H3 mast cells enhanced the nerve growth factor (NGF)-induced neuritogenesis of PC12 cells, we attempted to isolate an active compound from the mast cell conditioned culture medium. Our experiment identified 15-deoxy-$\Delta^{12,14}$-$PGJ_2$ (15d-$PGJ_2$), one of the $PGD_2$ metabolites, as a potential enhancer of neuritogenesis. 15d-$PGJ_2$ strongly enhanced the neuritogenesis elicited by a low-concentration of NGF that alone was insufficient to induce the neuronal differentiation. This 15d-$PGJ_2$ effect was exerted in a $Ca^{2+}$-dependent manner, but independently of the NGF receptor TrkA. Importantly, 15d-$PGJ_2$ activated the transient receptor potential vanilloid-type 1 (TRPV1), a non-selective cation channel, leading to the $Ca^{2+}$ influx. In addition, we observed that (i) NGF promoted the insertion of TRPV1 into the cell surface membrane and (ii) 15d-$PGJ_2$ covalently bound to TRPV1. These findings suggest that the NGF/15d-$PGJ_2$-induced neuritogenesis may be regulated by two sets of mechanisms, one for the translocation of TRPV1 into the cell surface by NGF and one for the activation of TRPV1 by 15d-$PGJ_2$. Thus, there is most likely a link between allergic inflammation and activation of the neuronal differentiation.**

Mast cells are some of the principal effector cells involved in the pathogenesis of allergic diseases and in certain host responses against infection. The roles of mast cells in mediating an allergic reaction are well understood. The aggregation of the high affinity IgE receptor (FcεRI) on mast cells by allergen/antigen results in the rapid release of pro-inflammatory mediators. This is followed by a delayed phase of mast cell activation resulting in the production and secretion of cytokines and chemokines that recruit other immune cells, such as lymphocytes and eosinophils, leading to chronic inflammation[1]. Although the view that mast cells are primarily involved in the immune responses has been prevalent[2], there is increasing evidence that mast cells participate in other physiological processes such as nervous system functions[3].

The activation of mast cells leads to the rapid production of a large variety of mediators, such as prostaglandins (PGs)[4,5]. $PGD_2$ is known to be one of the major PGs produced from mast cells, which has significant effects on a number of biological processes, such as platelet aggregation, relaxation of smooth muscles, and nerve cell functions. $PGD_2$ also exerts its allergic inflammatory effects, including blood flow changes, influx of Th2 lymphocytes and eosinophils, and induction of Th2 cytokine production, through high affinity interactions with the G-protein coupled receptors DP1 and chemoattractant-homologous receptor expressed on T-helper type 2 cells (CRTH2). Both receptors act in concert to facilitate a variety of biological functions involved in the development and maintenance of the allergic response[6,7]. Meanwhile, $PGD_2$ is a relatively unstable molecule. $PGD_2$ readily undergoes spontaneous dehydration in aqueous media to yield biologically active cyclopentenone PGs of the $J_2$ series, such as $PGJ_2$, $\Delta^{12,14}$-$PGJ_2$, and 15d-$PGJ_2$[8–10]. Unlike other classes of prostanoids, the J-series PGs have their own unique spectrum of biological effects, including anti-inflammatory effects[11,12] and an agonistic effect on the peroxisome proliferator-activated receptor γ (PPARγ)[13,14].

[1]Graduate School of Bioagricultural Sciences, Nagoya University, Nagoya 464-8601, Japan. [2]PRESTO, Japan Science and Technology Agency (JST), Kawaguchi, Saitama 332-0012, Japan. [3]Laboratory of Molecular Biology, Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Kyoto 615-8510, Japan. Correspondence and requests for materials should be addressed to K.U. (email: uchidak@agr.nagoya-u.ac.jp)