A plausible involvement of plasmalemmal voltage-dependent anion channel in the neurotoxicity of 15-deoxy- $\Delta^{12,14}$ -prostaglandin J₂

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BACKGROUND: Voltage-dependent anion channels (VDACs) are small, abundant in the outer mitochondrial membrane. VDAC has a crucial role in apoptotic mitochondrial changes by interacting with Bax/Bak and Bcl-xL. VDAC has been reported to be not only expressed in mitochondria but also plasma membrane. In the central nervous system, we have been proposing 15-deoxy- $\Delta^{12,14}$ -prostaglandin J₂ (15d-PGJ₂) as one of neurodegenerative mediator. Chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2) and peroxysome-proliferator activated receptor γ (PPAR γ) are membrane receptor and nuclear receptor of 15d-PGJ₂, respectively. 15d-PGJ₂ induces neuronal apoptosis independently of CRTH2 and PPAR γ . It has not yet been sufficiently clarified how 15d-PGJ₂ elicits its neurotoxicity. Here, we found VDAC as one of membrane receptor candidates. Therefore, we examined how VDAC could be involved in the 15d-PGJ₂-induced neuronal apoptosis.

METHODS AND RESULTS: VDAC was identified as a membrane target of 15d-PGJ₂ by proteomic approach. The binding of VDAC with 15d-PGJ₂ was detected by pull-down assay. In the primary culture of rat cortical neurons, VDAC was localized on the neuronal cell surface by immunostaining. Plasmalemmal VDAC (pl-VDAC) was co-localized with membrane targets of 15d-PGJ₂. To target only pl-VDAC, but not mitochondrial one, the anti-VDAC antibody was applied to primary neurons without permeabilization. Neither normal IgG nor the anti-VDAC antibody affected neuronal cell survival by evaluating cell viability with MTT-reducing activity. 15d-PGJ₂ activated caspase-3, resulting in neuronal apoptosis. The anti-VDAC antibody attenuated the neurotoxicity of 15d-PGJ₂ partially but significantly. Furthermore, the antibody reduced the 15d-PGJ₂-stimulated caspase-3 activity.

CONCLUSION: We confirmed that VDACs were not only expressed in mitochondria but also neuronal plasma membrane. Plasmalemmal VDAC was identified as a membrane target of 15d-PGJ₂, suggesting the plausible involvement in the neurotoxicity of 15d-PGJ₂.