

Outline

Our laboratory discovered that the causative agent of ginkgo poisoning is a vitamin B6 derivative, and we are currently focusing on research into the pharmacokinetics of vitamins.

Overconsumption of *Ginkgo biloba* seeds induces food poisoning. The main symptoms of *Ginkgo biloba* seed poisoning are tonic and/or clonic convulsion and vomiting. Our group demonstrated that 4'-O-methylpyridoxine (MPN) is responsible for food poisoning by *Ginkgo biloba* seeds (Wada *et al.*, 1985). Plasma MPN concentration in patients who suffered from the poisoning is analyzed by HPLC in our laboratory in response to the doctor's request. MPN inhibits enzymatic activation of vitamin B₆, resulting in vitamin B₆ deficiency and leading to diminished γ -aminobutyric acid (GABA) synthesis (Fig. 1, Kobayashi *et al.*, 2015). Since the food poisoning has occurred frequently in children under six years of age (Fig. 2, Kobayashi *et al.*, 2014), the mechanism of age-related sensitivity to MPN is being studied in our laboratory.

Recently, it has been reported that glycosylphosphatidylinositol (GPI)-anchored proteins, alkaline phosphatase and CD73, are important for the cellular uptake of the active form of vitamin B2 in addition to vitamin B6 (Fig. 3, Shichinohe *et al.*, 2022, Akiyama *et al.*, 2018).

Faculty members

Professor : Naoya HAMAUE, Ph.D.

Associate professor : Daisuke KOBAYASHI, Ph.D.

Assistant professor : Toshiki YAMASHIRO, Ph.D.

Main research in progress

- 1) Epidemiological investigation of food poisoning by *Ginkgo biloba* seeds (Mei *et al.*, 2017, Kobayashi *et al.*, 2019)
- 2) Diagnostic assay of MPN and vitamin B₆ analogues in biological specimen (plasma, serum, cerebral spinal fluid or urine) of patient of food poisoning by *Ginkgo biloba* seeds (Sado *et al.*, 2019, Azuma *et al.*, 2020)
- 3) Metabolisms of 4'-O-methylpyridoxine and their contribution of MPN toxicity
- 4) Vitamin metabolism in patient with Hypophosphatasia (Akiyama *et al.*, 2018)
- 5) Activation and inactivation mechanisms of vitamins (Shichinohe *et al.*, 2022)

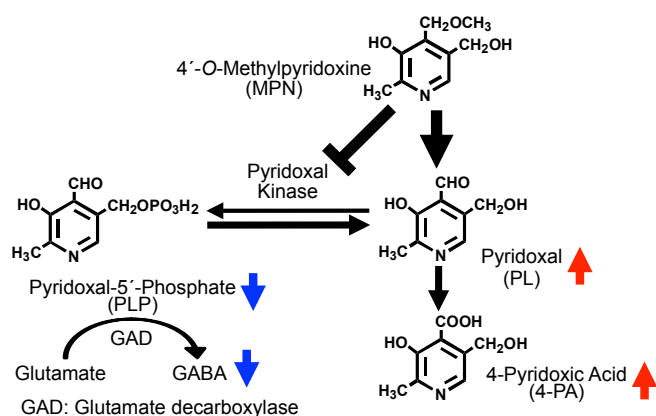


Fig. 1 Effects of 4'-O-methylpyridoxine on vitamin B₆ activation pathway and GABA synthesis. (Kobayashi *et al.*, 2015)

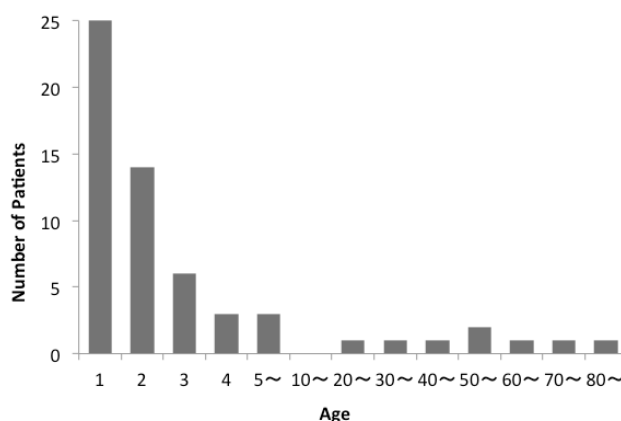


Fig. 2 Age-specific numbers of patients with food poisoning by *Ginkgo biloba* seeds in Japan. (Kobayashi *et al.*, 2014)

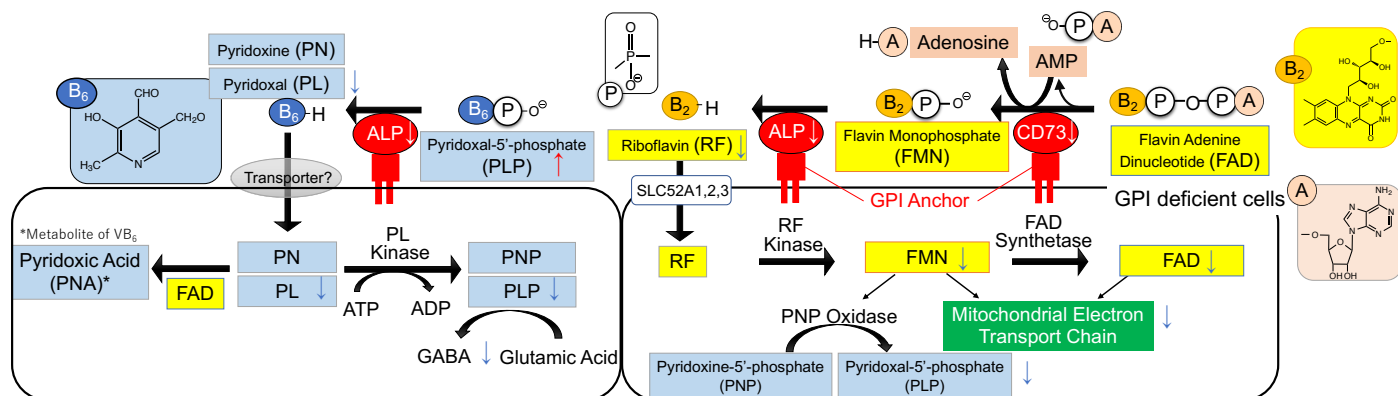


Fig. 3 GPI-anchored proteins (ALP and CD73) involved in cellular uptake of vitamin B2 and B6, vitamin or amino acid metabolism and mitochondria function (Shichinohe et al., 2022)

Current publications

- Kobayashi D, Yoshimura T, Johno A, Ishikawa M, Sasaki K & Wada K, Decrease in pyridoxal-5'-phosphate concentration and increase in pyridoxal concentration in rat plasma by 4'-O-methylpyridoxine administration, *Nutr Res*, **35**: 637-642(2015).
- Mei N, Guo X, Ren Z, Kobayashi D, Wada K & Guo L, Review of *Ginkgo biloba*-induced toxicity, from experimental studies to human case reports, *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev*, **35**: 1-28 (2017).
- Akiyama T, Kubota T, Ozono K, Michigami T, Kobayashi D, Takeyari S, Sugiyama Y, Noda M, Harada D, Namba N, Suzuki A, Utoyama M, Kitanaka S, Uematsu M, Mitani Y, Matsunami K, Takishima S, Ogawa E & Kobayashi K, Pyridoxal 5'-phosphate and related metabolites in hypophosphatasia: Effects of enzyme replacement therapy, *Mol Genet Metab*, **125**: 174-180(2018).
- Kobayashi D, Food Poisoning by *Ginkgo* Seeds through Vitamin B6 Depletion (Japanese), *Yakugaku Zasshi*, **139**: 1-6 (2019).
- Sado T, Nakata S, Tsuno T, Sato M, Misawa Y, Yamauchi S, Inaba Y, Kobayashi D & Wada K, Concentrations of various forms of vitamin B6 in ginkgo seed poisoning. *Brain Dev*, **41**: 292-295(2019).
- Azuma F, Nokura K, Kako T, Kobayashi D, Yoshimura T, Wada K., An Adult Case of Generalized Convulsions Caused by the Ingestion of *Ginkgo biloba* Seeds with Alcohol. *Intern Med*, **59**: 1555-1558(2020).
- Shichinohe N, Kobayashi D, Izumi A, Hatanaka K, Fujita R, Kinoshita T, Inoue N, Hamaue N, Wada K, Murakami Y, Sequential hydrolysis of FAD by ecto-5' nucleotidase CD73 and alkaline phosphatase is required for uptake of vitamin B2 into cells. *J Biol Chem*, **298**: 102640(2022).

Contact e-mail address

kobadai@hoku-iryo-u.ac.jp