

ABSTRACT AGA DDW Mai 2017

Characterization of titanium dioxide nanoparticle intestinal absorption, in vivo and ex vivo, in the mouse.

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Background : Titanium dioxide (TiO₂) nanoparticles are ingested on a daily basis by millions of people, especially in western countries, being largely used as additive in manufactured foods or pharmaceutical drugs. Its oral administration was shown to exacerbate colitis, during UC or Crohn Diseases, by activating the NLRP3 inflammasome in gut and increasing its overall distribution in the blood or the spleen (Lomer MC Br J Nutr 2004;92:947, Ruiz PA, [Gut](#). 2016 Feb 4. pii: gutjnl-2015-310297).

Methods : Our study investigated the intestinal absorptive route of the alimentary TiO₂ (E171) , after a unique gavage in mice, characterizing the major sites and kinetic of its absorption and distribution in the intestine and blood. The pathways of TiO₂ absorption were also characterized ex vivo, in anesthetized mouse using specific inhibitors injected with the particles in ligatured loops of the jejunum. The TiO₂ particles were detected using confocal microscopy and laser light reflection which uniquely permit to look at extended tissue area.

Results : The TiO₂ particles from 100 nm to 1-2 micrometers showed a major absorption in the jejunum in both the villi and Peyer Patches and much lower uptake in ileon and colon. In villi the TiO₂ absorption rose until 4 hours after feeding and returned to control levels at 8 h while Peyer patches contents remained low at 4h but are significantly increased at 8 h. TiO₂ particles were also 4 time increased in the blood at 4 and 8 h, compared to controls, showing similar kinetics of accumulations as previously reported in human (Pele, L. C. et al. Part Fibre Toxicol, 2015 **12**, 26). In *ex vivo* experiments the absorption of TiO₂ in ligatured loops of jejunum were found to be rapid, clearly visible after 15 or 30 minutes of incubation and is inhibited by 66 % in the presence of 100 mM of TAP (4,5,6-Triaminopyrimidine sulfate) a tight junction blocker suggesting a major absorption via a paracellular pathways across epithelial tight junctions. By contrast, the intestinal uptake of TiO₂ was not modified in the presence of either 100 mM 5-(N-Ethyl-N-isopropyl) amiloride inhibiting pinocytosis, 30 μM pitstop 2 which blocks clathrin dependent endocytosis or 17 μM methyl beta-cyclodextrin affecting raft-mediated endocytosis, showing little or no contribution of endocytosis in the absorptive process.

Conclusion : We developed an easy method to rapidly follow the intestinal absorption of TiO₂ by the intestine using confocal microscopy. The absorption occurred through out the intestine, being predominant in both villi and Peyer patches of the jejunum. Most TiO₂ particles entered the intestine through a paracellular route, passed through it and were transferred to the blood in a few hours.