

EXCESS FLUORIDE INTERFERENCE WITH CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR (CFTR)

SUMMARY: Recent research has demonstrated that transport of excess fluoride in cystic fibrosis (CF) occurs in the mutated transmembrane conductance channel regulator (CFTR). Since disturbances in these channels are responsible for the symptoms associated with CF, this knowledge that fluoride is also transported through these channels opens ways to achieve a better understanding of how fluoride exacerbates the symptoms of CF or induces CF-like symptoms in individuals without the CFTR genetic anomaly.

Keywords: Ameloblasts; CFTR; Cystic fibrosis; Fluoride transport; Transmembrane conductance.

Cystic fibrosis (CF) is one of the most common, lethal, genetically transmitted diseases in Caucasians, affecting approximately 1 in every 2,500 newborns, with few surviving past middle-age adulthood.¹ The disease is caused by mutation in the gene responsible for regulating the movement of chloride, water, and other vitally important biological entities, leading to abnormalities in sweat, mucus, and digestive juices. CF is characterized by the accumulation of thick, sticky mucus in the lungs, pancreas, and digestive tract. The accumulated mucus clogs the air passages in the lungs, making breathing difficult, and leads to frequent lung infections. Pancreatic insufficiency leaves the patient unable to create the enzymes necessary for proper digestion, while the accumulation of mucus in the digestive tract prevents the pancreatic enzymes from reaching the food in the gut, leading to serious nutrient deficiencies.

In 1989, the mutated gene in CF was identified and named cystic fibrosis transmembrane conductance regulator (CFTR).² The CFTR chloride channel belongs to the superfamily of the ATP-binding cassette (ABC) transporters, which bind ATP and use the energy to drive the transport of a wide variety of substrates across extra- and intracellular membranes.³ CFTR also regulates the activity of other channels and transporters. The tissues affected by CF include sweat glands, intestines, pancreas, bile ducts, respiratory epithelia, submandibular glands, uterus, skeletal muscle and vas deferens.⁴

It is now known that bone and dental enamel, a product of epithelial cells, are also affected in individuals with CF, causing some of them to develop reduced bone density (osteopenia) and dental defects. Recently, Bronckers et al. provided evidence that CFTR is also expressed in maturation stage ameloblasts (enamel-secreting cells of teeth), odontoblasts (layer of cells lining the pulp cavity of a tooth, from which dentin is formed), and in bone cells.⁴ Their work demonstrates that the CFTR is probably active in the pH regulation of maturation ameloblasts, and is essential for the completion of enamel mineralization. CFTR regulates pH because ameloblasts are permeable to bicarbonate and are involved in the exchange of extracellular chloride with intracellular bicarbonate.

Endocytosis is the process by which plasma membrane folds inward to create a membrane-bound transportation vehicle (vacuoles) for the movement of substances into the cell. Fluoride has been shown to reduce the function of this essential transportation system in kidney and colon.^{5,6} The recent 2011 paper by

Duan et al. concludes that excess fluoride, in millimolar concentrations of an ameloblast system, inhibits the endocytic activity (transport of proteins) of ameloblasts through perturbations in the CFTR chloride channel.⁷ Although CFTR has a high affinity for bromide and chloride, it has been found in this *in vitro* experiment that fluoride ion also competes for transport in these channels.⁷ The accumulation of fluoride might result in toxicity to ameloblasts. Defective CFTR function seems to result in pathological endocytosis in ameloblasts, leading to increased protein content in mature enamel. We now need *in vivo* research to determine what range of fluoride intake may disturb this important cellular system.

Earlier research by Hardin et al. demonstrated that transport of bovine serum albumin was significantly inhibited with sodium fluoride.⁵ Since transport of molecules is an energy dependent process, studies by Schmid et al. demonstrating that ATP is required for receptor-mediated endocytosis are also relevant.⁶ It is also well established that fluoride, in combination with aluminum (AlF_x),⁸ disturbs G protein function by acting as a phosphate mimic. This may result in reduced availability of cellular energy required for these cellular functions.

These papers suggest that fluoride may exacerbate symptoms of CF and may induce CF-like symptoms in those without the CFTR genetic anomaly by causing perturbations in the regulation of genetically normal transmembrane conductance channels. The CFTR proteins are found in both cell membranes and membranes of intracellular organelles, thus demonstrating their widespread importance in the regulation of cellular homeostasis. Given the fact that fluoride is now known to be transported through these channels, it is important to understand the mechanisms by which fluoride may potentially impact all tissues containing these or similar chloride channels.

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