Fluorine and Thyroid Gland Function: A Review of the Literature

H. Bürgi, L. Siebenhüner, and E. Miloni
Medizinische Klinik am Bürgerspital, Solothurn und Laboratorium für Endokrinologie der Medizinischen Universitätsklinik Inselspital, Bern, Schweiz

Summary. The increasing use of fluoride for prevention of dental caries poses the problem as to whether this halogen has antagonistic properties towards iodine, whereby it could hamper the success of iodine prophylaxis of endemic goitre. Review of the literature shows that some authors have found an inhibition by fluoride of various steps of thyroid hormone biosynthesis in animal experiments. By and large, the inhibition was only slight and it was elicited only with fluoride doses greatly in excess of those recommended for caries prevention. The inhibition was not consistently present and other authors could not confirm it in comparable experiments. There is no convincing evidence that fluoride produces true goitres with epithelial hyperplasia in experimental animals. There are some reports based on casual observations that fluoride is goitrogenic in man. On the other hand, several good studies with adequate exposed and control populations failed to detect any goitrogenic effect of fluoride in man. It is noteworthy in particular that fluoride does not potentiate the consequences of iodine deficiency in populations with a borderline or low iodine intake. Published data fail to support the view that fluoride, in doses recommended for caries prevention, adversely affects the thyroid.

Key words: Fluorine – Thyroid gland – Goitre

Fluorine is an element of the halogen series, and it has been suspected that this might confer to it antagonistic properties towards iodine, another halogen. Study of the literature reveals that thyroidal effects of fluoride are very controversial. Numerous publications on this subject are scattered over decades in journals covering various fields such as endocrinology, dental medicine, industrial medicine, toxicology and nutrition. A review seems therefore appropriate, in particular in view of the continuing problem of endemic goitre [28] and the growing use of fluoride for caries prevention [52, 63]. Several countries, such as Mexico and Switzerland, have engaged on double preventive programs by adding to domestic salt both iodine and fluoride [52]. Should the latter prove antagonistic to the former, goitre eradication programs might be compromised.

In the publications reviewed below fluoride exposure differed greatly in fluoride compound, dose and length of exposure. Wherever the data permitted, we have made an effort to calculate the daily dose and to express it in mg fluoride. When a salt was given, the term fluoride is used. When fluoride was given in another or non-specified form (e.g. rock phosphate) the term fluorine was chosen. As will be seen, most experimental work used relatively high doses of fluoride, in most cases vastly in excess of the 1–2 mg/day and person which are recommended for caries prevention. Starting with the metabolism of fluoride by the thyroid gland, the review will cover fluoride actions on the various steps of thyroid hormone biosynthesis in logical sequence, to end with an analysis of its effects on goitrogenesis. Several critical previous reviews are available [12, 26, 43, 61].

Fluorine Metabolism by the Thyroid Gland

Normal or goitrous human thyroid glands obtained from several areas of Switzerland contained 2.2–57 μg fluoride/g dry weight [15]. Glands from hyperthyroid patients removed surgically contained 1.5–95 μg fluoride/g dry weight [14]. When fluoride-containing phosphate is mixed in cow feed for 6 months the fluorine in the thyroid rises from 6.8 to 164 μg per g dry weight, as compared with
a final concentration of 8.1 μg/g in liver and 1,640 μg/g in bone [6]. Rats consuming 0.9 mg fluoride/day for 20 weeks accumulate 14 μg fluorine per thyroid gland which gives an estimated concentration of 6,000 μg/g dry weight compared to 10,000-16,000 μg/g dry weight in bone [58]. Other authors however found undetectable levels (i.e. less than 20 μg/g wet tissue) of fluorine in the thyroid gland of rats that had consumed water containing 20 mg/l fluoride for 11 months, despite a marked accumulation to 1,850 μg/g in bone [2].

It is unknown in what form the fluorine is stored in the thyroid, or how it is concentrated there. In Wadhwani's [58] experiment cited above the fluorine content was 16 μg/g in blood and 720 μg/g (wet, estimated by assuming a thyroid weight of 12.5 mg) in the thyroid gland of rats. This suggests that the high thyroidal fluorine content cannot be explained by simple diffusion from blood.

Experiments with radioactive fluorine show that fluoride ion, contrary to a widely held belief and unlike iodide ion, is not actively transported into the thyroid gland of humans [16, 17] or rats [59]. Hein [25] claims that 18F− was actively accumulated in thyroid tissue of rats. Analysis of his data shows rather that the 18F− concentration in the thyroid, albeit higher than in other organs such as heart muscle or liver (which seem to exclude fluoride), is never higher than in blood.

In summary the available data tend to agree that fluoride ion is not concentrated by the thyroid gland [67]. After long-term fluorine exposure however, several studies have found surprisingly high levels of fluorine in the thyroid gland. Unfortunately fluorine measurements are fraught with technical difficulties in some tissues [15]. Moreover, it is unknown in what form (ionic or organic) fluorine might accumulate in the thyroid gland. These two problems probably account for the discrepant fluorine concentrations found by different investigators. Unfortunately, 18F, the only available isotope, has such a short half-life (112 min) as to preclude any long-term isotope experiments.

**Fluoride Effects on In vitro Thyroid Metabolism**

In thyroid slices of various species 2–10 mM NaF stimulate adenylate cyclase, glucose oxidation, organic binding of iodide and phosphate incorporation into phospholipids, thus mimicking the effects of thyrotropin [1, 48, 51, 64, 68]. Strangely enough, this stimulatory fluoride effect is accompanied by a rise in the intracellular messenger cyclic adenosine monophosphate (AMP) only in homogenates, but not in slices [1, 48, 51]. Moreover, fluoride, contrary to thyrotropin, inhibits colloid endocytosis and hormone secretion in slices [48, 51, 64]. It is doubtful therefore that these in vitro fluoride effects are mediated by cyclic AMP. Thus, fluoride effects on the in vitro metabolism of thyroid and other tissues [30] are well established, but it is unlikely that the necessary plasma fluoride levels of 2–10 mM (40–190 μg/ml) can be reached in vivo, since the plasma concentration in our experiment with the highest tolerated dose was only 0.57 μg/ml, and the thyroid gland does not actively concentrate fluoride ion. On the other hand, we must concede that some investigators found fluoride levels of up to 6,000 μg/g dry thyroid weight in exposed animals (see preceding section) but the chemical state of this thyroidal fluorine is unknown and might well be in an organic compound. The effects or toxicity are therefore difficult to guess.

In a simple system containing no tissue components Minder and Gordonoff [21, 44] found that diiodotyrosine in aqueous solution deiodinated faster to monoiiodotyrosine in the presence of equimolar fluoride. This purely chemical experiment has little biological meaning in our opinion, but the authors used it as evidence for an antithyroid effect of fluoride and as the main argument for their vehement opposition to the use of fluoride for caries prevention [20].

**Fluoride Effects on Thyroidal Iodine Content and Radioiodine Turnover**

Volunteer persons receiving 1.5–5 mg fluoride daily had a slightly increased thyroidal 131I uptake on the 5 mg dose after 4 weeks [34], but the effect seemed to be no longer demonstrable after 2–5 months [35, 37]. In 26 men suffering from chronic industrial fluorosis in the German Democratic Republic the mean thyroidal radioiodine uptake was significantly higher than in controls [27]; it must, however, be added that the uptake was high already in controls, due to known prevailing iodine deficiency.

In rats ingesting 0.225 mg [20] or 2 mg fluoride/day or injected acutely with 2 mg fluoride [33] the thyroidal radioiodine uptake was decreased. In the acute test, moreover, organification of the transported iodide and its incorporation into diiodotyrosine and thyroxine were diminished [33]. Contrary to this, several other studies in rats and rabbits found unchanged uptakes when 2 mg fluoride was injected acutely [23] or given chronically in