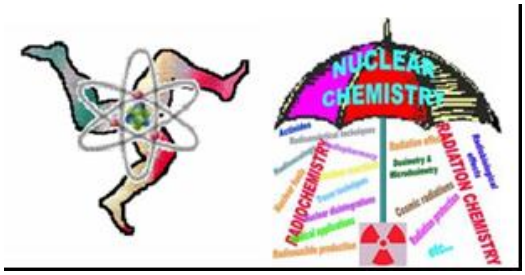

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Radiopharmacological studies: interaction of antidepressant fluoxetine with thyroid hormones metabolism

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Using [I-125]-labeled iodothyronines as substrates, we applied our newly developed radiometric enzyme assays for iodothyronine deiodinases (IDs) of types 1, 2 and 3 (D1, D2 and D3), as well as the adapted radiometric assays for conjugating enzymes uridine 5'-diphospho-glucuronyltransferase (UDP-GT) and iodothyronine sulfotransferases (ST), in radiopharmacological studies of the interaction of an antidepressant drug fluoxetine (Fluox) with the metabolism of thyroid hormones (TH) in the rat.
TH are supposed to control the activity of some neurotransmitters (e.g., serotonin), which are hypothetically involved in the pathogenesis of depressive illness. Inadequate activities of brain IDs could lead to local insufficient triiodothyronine concentration and might be, therefore, one of the pathogenic factors of depression. Conjugation of phenolic hydroxyl group of hydrophobic TH with UDP-glucuronic acid (catalyzed by UDP-GT) or with sulfate (catalyzed by ST) should lead to their increased water solubility and increased excretion in bile and/or urine and, therefore, to decreased TH plasma levels.
The effects of subchronic administration (for 25 days) to Wistar rats of Fluox by itself (1.5 to 6 mg per animal per day) or 3,3´,5-triiodo-L-thyronine (T3) (10 micro g per animal per day) by itself or in combination with Fluox, on T3 production and degradation in the CNS and in different peripheral rat tissues were followed both, at the level of whole organism and at the molecular level.
At the whole-body level, we found that administration of fluoxetine caused a slight decrease in serum total thyroxine (T4) levels, but produced only a negligible effect on T3 levels. The treatment of rats with supraphysiological amounts of T3 caused very marked decline of serum T4 levels, due to a feedback action of TH. Surprisingly, administration of Fluox together with supraphysiological amounts of T3 caused a distinctive fall of non-physiologically high concentrations of serum T3, which were reached by giving the animals the same amounts of T3 alone, to nearly normal levels.
The elaborated radiometric assays for IDs, UDP-GT and ST were found usable for the assessment of enzymatic changes, at the molecular level. About two-fold higher UDP-GT activities were found in liver microsomes of the rats treated with Fluox in comparison with control rats. On the contrary, the enzyme activities of ST in the liver and kidney cytosolic fractions of the control and treated animals were found to be negligible and not influenced by the treatments. However, changes in IDs activities caused by the treatment of rats with Fluox alone, and especially with T3 by itself were much more pronounced and could be easily quantitated.
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