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Effect of sex hormones on *n*-3 polyunsaturated fatty acid metabolism and FADS2 mRNA expression in HepG2 cells

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Women aged less than 40 have higher docosahexaenoic acid (22:6*n*-3) status[(1)] and convert more α-linolenic acid (18:3*n*-3) to longer chain *n*-3 polyunsaturated fatty acids (PUFA) than men[(2)]. Sex hormones have been implicated as regulators of PUFA biosynthesis. Hormone replacement therapy and the oral contraceptive pill use has been shown to increase plasma 22:6*n*-3 concentration in post and pre-menopausal women respectively,[(3)] and to increase 22:6*n*-3 synthesis[(1)]. The nature of the regulation of PUFA synthesis by sex hormones is unclear, however, there is evidence of an effect on the mRNA expression of FADS2, which encodes the rate limiting enzyme Δ6 desaturase[(4,5)]. Characterisation of the mechanism is important for understanding how hormones influence dietary requirements for *n*-3 PUFA. Here we investigated the effect of sex hormones on the conversion of 18:3*n*-3 and on the FADS2 mRNA expression in human hepatic carcinoma cells.

To measure the effect of sex hormones on 18:3*n*-3 metabolism, HepG2 cells were incubated for 48 hours with 10 μM [d_5]18:3*n*-3 and physiological concentrations of EE_2 (7 nM), progesterone (50 nM) or testosterone (50 nM), or no hormone supplement (untreated). [d_5] Incorporation into *n*-3 PUFA was determined by GC[(6)] and by GC-MS[(7)]. The mass of labelled fatty acids was normalised to total cell protein content. FADS2 mRNA expression was measured by incubating HepG2 cells for 72 hours with hormones at the above concentrations. FADS2 mRNA expression was measured by real-time RT-PCR[(8)].

Treatment of HepG2 cells with progesterone, but not EE_2, decreased the amount of [d5]18: 3*n*-3 significantly and increased the amount of 20:5*n*-3, 22:5*n*-3 and 22:6*n*-3 (all $P<0.0001$) compared to untreated cells (Figure). There was a small increase in the amount of 22:5*n*-3 in testosterone-treated cells. Progesterone, but not EE_2 or testosterone, significantly increased mRNA expression of FADS2 ($P<0.001$), compared to untreated cells (Figure).

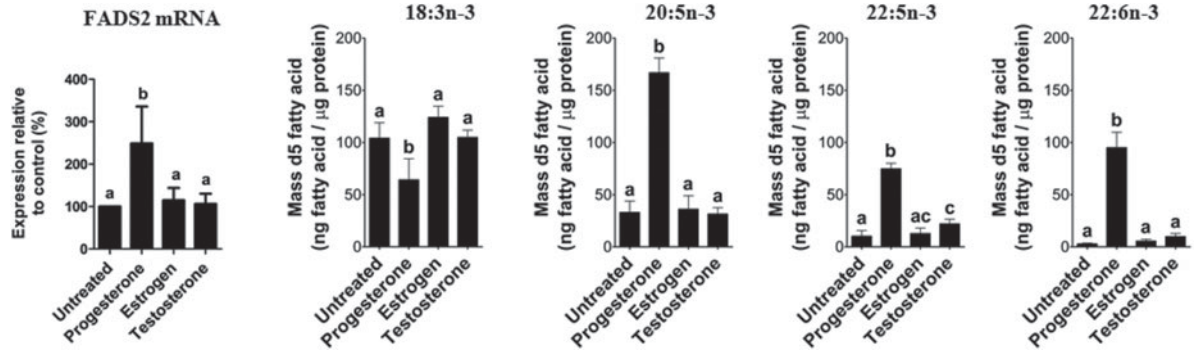

Fig. 1. FADS2 mRNA expression relative to untreated (set at 100%) and mass of d_5 18:3*n*-3, 20:5*n*-3, 22:5*n*-3 and 22:6*n*-3. Values are mean (SD). Data were analysed by 1-way ANOVA with Bonferroni's post hoc test. Means with different letters differed significantly ($P<0.05$)

Together these findings show that progesterone increases conversion of 18:3*n*-3 to longer-chain metabolites. This was associated with increased FADS2 mRNA expression, which suggests that this hormone may act by regulating FADS2 transcription. These results are in agreement with a previous reports of the effect of mixed hormone supplements in women[(1,3)] and with the observation that progesterone concentration was associated positively with FADS2 mRNA expression in pregnant rats[(5)]. Overall, these findings show, for the first time, a direct effect of a specific sex hormone acting via gene transcription on PUFA metabolism.

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