

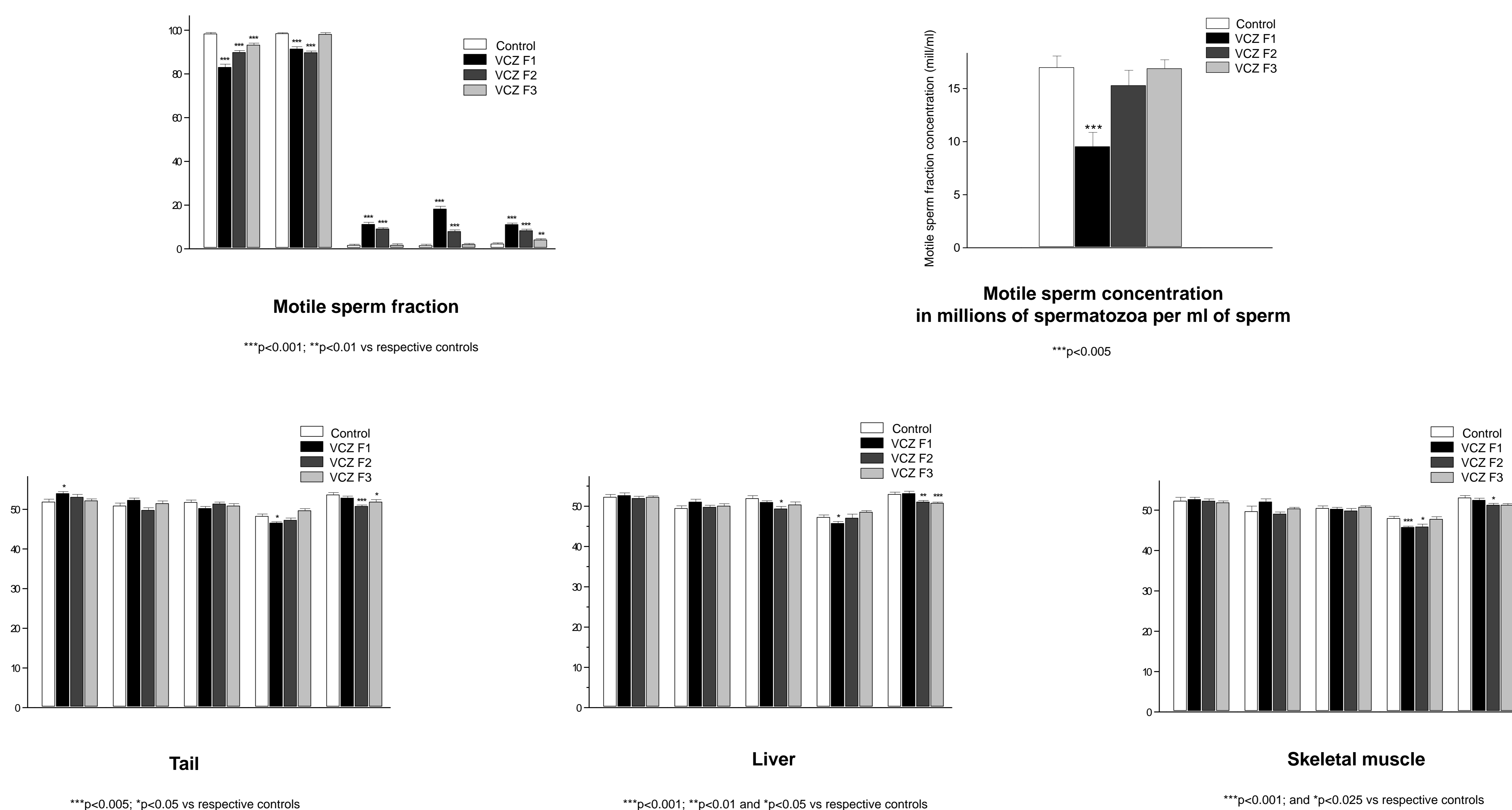
Transgenerational effects of the endocrine disruptor vinclozolin on the methylation pattern of imprinted genes in the mouse sperm

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Endocrine-disrupting chemicals (EDCs), among which the antiandrogen vinclozolin (VCZ), have been reported to affect the male reproductive system. In this study, VCZ was administered to pregnant mice at the time of embryo sex determination and its possible effects on the differentially methylated domains (DMDs) of 2 paternally (H19 and Gtl2) and 3 maternally (Peg1, Snrpn and Peg3) imprinted genes were tested in the male offspring. The CpGs methylation status within the 5 gene DMDs was analyzed in the sperm, tail, liver and skeletal muscle DNAs by pyrosequencing.



Results

In the sperm of controls, the percentages of methylated CpGs were close to the theoretical values of 100% and 0% in paternally or maternally imprinted genes, respectively. VCZ decreased the percentages of methylated CpGs of H19 and Gtl2 (respective values 83.1 and 91.5%) and increased those of Peg1, Snrpn and Peg3 (respective values 11.3, 18.3 and 11.2%). The effects of VCZ were transgenerational but disappeared gradually from F1 to F3. The mean sperm concentration of the VCZ-administered female offspring was only 56% of that of the controls in the F1 and back to normal values in the F2 and F3 offspring. In the somatic cells of controls, the percentages of methylated CpGs were close to the theoretical value of 50% and, surprisingly, VCZ altered the methylation of Peg3. We propose that the deleterious effects of VCZ on the male reproductive system are mediated by imprinting defects in the sperm. The reported effects of EDCs on human male spermatogenesis might be mediated by analogous imprinting alterations.

VCZ administration to pregnant female mice induces alterations in the methylation pattern of 5 imprinted genes (H19, Gtl2, Snrpn, Peg1, Peg3) in the sperm of the offspring which disappear gradually from F1 to F3.

The reported effects of endocrine-disrupting chemicals (EDCs) on human male spermatogenesis and fertility rates might involve imprinting alterations in the sperm.