Gestational and postnatal exposures to dietary low doses of genistein and/or vinclozolin in rodents: effects at different developmental steps, modes of action, compounds fate and biotransformaion in various organs and tissues

J. Auger[1,*], MC. Canivenc-Lavier[2], M. Perrot-Applanat[3], R. Habert[4], JF. Savouret[5] and JP. Cravedi[6]

[1] Service de Biologie de la Reproduction, Hôpital Cochin, Paris, [2] INRA UMR 1129 FLAVIC, Dijon, [3] U553 INSERM, Hôpital St Louis, Paris, [4] U566 INSERM/ CEA, Université Paris 7, Fontenay aux Roses, [5] INSERM UMR-S530, Université Paris 5, Paris, [6] INRA/ENVT UMR 1089 Xénobiotiques, Toulouse. *e-mail: jacques.auger@cch.aphp.fr

A preliminary study in the rat investigating the male reproductive effects of an exposure to the phytoestrogen genistein and the antiandrogenic fungicide vinclozolin with a design approximating real world exposures (low doses, 1mg/kg/day for each, dietary exposure from conception to adulthood) has indicated numerous detrimental effects of the compounds, and more markedly their mixture, on the male reproductive tract and fertility.

Starting from a similar experimental design, the main objective of the present multidisciplinary project was the investigation of the effects and mechanisms of action of low-dose genistein and/or vinclozolin in several organs and tissues according to whether the exposure was gestational/lactational or from prepuberty to adulthood.

The program was based on main exposure protocols in the rat (similar to the protocol used in the pilot study) and side experiments using a number of molecular, cellular or analytical approaches.

In utero vinclozolin exposure decreases the number of gonocytes in the neonatal period. This does not seem to result in modified sperm production. Overall, gestation/lactation exposure to genistein and/or vinclozolin does not affect the steroidogenesis in the neonatal period. Developmental anomalies of the male reproductive tract, mainly undescended testis, are observed for about one third of animals exposed to the mixture.

Pups continue to be exposed to both compounds during the lactation. Vinclozolin is not detected in milk or pups plasma: M1 and M2 vinclozolin metabolites are the active compounds detected. Gestation/lactation exposure to vinclozolin and to the mixture delays the male puberty onset. The three exposure modalities feminize the food behaviour of the males in the post-lactation period, alter the morphology and the maturity of the salivary glands with a gender effect and they severely disrupt the pubertal development of the mammary gland.

Diminished epididymal weights and decreased sperm numbers were found in the male adults exposed to genistein or vinclozolin from the postlactation period, while the most important anomaly found in the male adults that have been exposed during the gestation/lactation period was and increased rate of post-implantation loss after crossing with control females. Finally, several anomalies related to the cartilage, male genital tract and food behaviour have been observed in the second unexposed generation stemmed from exposed fathers.

At the low doses tested the modes of action in the tissues and organs studied appear noticeably complex, as illustrated by the modifications of the testis transcriptome in the adult, and their deciphering is still ongoing.

To our knowledge, this is the first multidisciplinary study providing evidence that low doses of genistein and/or vinclozolin, albeit not environmental for this last compound, are able to concomitantly disrupt the physiology of various organs and tissues mainly as the consequence of a gestational/lactational exposure but also after a chronic postlactational exposure.

References

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