Intracellular distribution and biological effects of Vinclozolin and its metabolites in a sex steroid-sensitive model of human prostate adenocarcinoma

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Recent concern for the possible effects of endocrine disrupting chemicals on humans and wildlife [1] has resulted in considerable interest in environmental contaminants, including pesticides, that affect aspects of reproduction and early development. Vinclozolin (VIN), a pesticide used to treat fungal infections in plant-derived foodstuffs, plants and grasses, causes abnormal male sexual development in rats [1]. As a result of its widespread use, the analysis of VIN on food samples has been incorporated into the US Food and Drug Administration Pesticide Residue Monitoring Program [2]. VIN can undergo chemical hydrolysis, photolysis or metabolic transformation by mammals and bacterial systems. Szeto *et al.* [2] isolated three hydrolysis products from aqueous buffers which were identified as 2-[[(3,5-dichlorophenyl)-carbamoyl]oxy]-2-methyl-3-butenoic acid (M1), 3'5'-dichloro-2-hydroxy-2-methylbut-3-enanilide (M2) and 3,5-dichloroaniline (M3). While specific metabolic pathways have been proposed for VIN, information on the *in vivo* disposition of VIN and its metabolites is limited, particularly in the target organs of mammalian species [3]. The two hydrolysis products of VIN, M1 and M2, are competitive antagonists of the androgen receptor (AR) [1]. AR antagonism by M1 and M2 can ultimately decrease androgen-dependent gene expression, resulting in adverse effects in developing, pubertal and adult male rats. Administration of VIN during the critical period of sexual differentiation resulted in sexual abnormalities expressed later in the adult male rat. Pregnant rats exposed to VIN at specific gestational stages had male offspring with a significant degree of morphological feminization and demasculinization [1]. The characterization of the role of VIN and its metabolites M1 and M2 in human cells, such as prostate cells, has received limited attention. This is due in part to analytical difficulties such as instability of VIN in aqueous media [4]. Prostate is a critical but neglected target in reproductive toxicology. Prostate function is critical for male fertility and its well-known oncological biomarker, the prostate-specific antigen (PSA), can be also used to monitor prostate epithelial human cells upon treatment with pharmaceutical drugs or natural bioactive compounds [5,6].
The objective of this study was to characterize the biological effects of VIN and its metabolites on prostate epithelium cells investigating i) their anti-androgenic ability to inhibit DHT-induced PSA secretion, and ii) their intracellular distribution, in presence or absence of sex steroid (DHT), To verify whether and to which extent VIN and its metabolites are able to enter the cell and to reach the nucleus, the target of their supposed transcriptional modulatory activity upon binding to sex steroid receptors. For this purpose we used the LNCaP human prostate cell line as a model system to investigate chemicals affecting prostate epithelium functionality by means of a tiered approach integrating two different toxicological endpoints, cell viability (MTS assay) and PSA secretion, using well established, widely used commercial assays. Data will be presented and discussed.

References

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