

Zyma D Perturbateur Endocrinien

Anne Sarrabay

Evaluation des effets de faibles doses d'un perturbateur endocrinien de référence, le flutamide, sur l'appareil reproducteur mâle du rat adulte Anne Sarrabay, 2015 Les perturbateurs endocriniens (PE) font l'objet d'une controverse scientifique à l'heure actuelle car, pour certains scientifiques, ces molécules n'auraient pas de seuil de toxicité et agiraient à de très faibles concentrations. Cette particularité proviendrait du fait que les PE, quelles que soient leurs origines, agissent sur les hormones et leurs récepteurs. A ce titre, ils seraient assujettis aux mêmes règles que les hormones endogènes. Leurs effets à de très faibles doses s'expliqueraient par la sensibilité des récepteurs hormonaux aux faibles fluctuations de concentrations. L'absence de seuil d'effet pour les PE s'expliquerait par différents mécanismes, dont des différences d'affinité suivant la concentration entre substrat et récepteur, qui engendreraient des effets doses non monotones. Un certain nombre de revues remettent en cause ces hypothèses et les observations qui les accompagnent. Elles indiquent notamment le fait que ces données manquent de répétitions, qu'elles sont principalement issues d'études *in vitro* ou sur des modèles d'organismes en développement et non-nécessairement misent en perspective avec des effets toxiques pour l'organisme. Ainsi ces données ne seraient pas suffisantes pour statuer dans ce débat. Dans ce contexte, afin d'apporter de nouvelles données expérimentales au débat, nous avons cherché à caractériser les effets aux faibles doses d'un PE de référence, le flutamide (FLU), sur l'appareil reproducteur du rat mâle adulte. Pour ce faire, nous avons conduit trois études successives au cours desquelles nous avons exposé des rats Wistar de 7 semaines à une large gamme de doses de FLU. La dose la plus forte est connue pour induire des lésions testiculaires et une atrophie de la prostate. Les autres doses correspondent à la NOAEL définie dans une étude publiée précédemment, et à cette valeur divisée par 10, 100 et 1000, ce qui correspond à des faibles doses selon la définition de l'OMS. Pour chaque étude, chaque groupe était composé de 16 animaux gavés quotidiennement pendant 28 jours. Ces études ont permis d'explorer différents paramètres. Dans le cadre de la caractérisation du mode d'action du flutamide sur le testicule (Exposition --> blocage des récepteurs aux androgènes de l'hypophyse --> augmentation de la LH circulante --> prolifération des cellules de Leydig --> Hyperplasie), nous avons montré que, pour chaque événement clé, l'effet dose est monotone et qu'il est possible de définir un seuil. Par ailleurs, nous proposons le Pdgfd, un facteur de croissance, comme médiateur de l'effet mitogène de la LH sur les cellules de Leydig. Pour la prostate, le mode d'action du flutamide n'étant pas complètement élucidé à ces niveaux de doses, le travail a été plus exploratoire. Afin d'expliquer, aux

niveaux moléculaire et cellulaire, l'origine de la baisse du poids des prostates induites par le flutamide dès 1 mg/kg/j, nous avons exploré trois hypothèses: (1) l'augmentation de l'apoptose, avec un test d'activité des caspases 3 et 9 qui montre une activité supérieure pour le groupe forte dose de 10 mg/kg/j de flutamide, (2) la diminution de la prolifération, avec un marquage ki67 qui ne montre pas de différence entre le groupe témoin et la forte dose, et enfin (3) la baisse de la fonction de sécrétion de la prostate, évaluée par un western blot dirigé contre la probasine qui montre une baisse de sa production. Dans le même temps, nous avons montré, au niveau des transcrits hépatiques (RT-qPCR), que le flutamide exerce un effet-dose monotone sur certaines enzymes impliquées dans le métabolisme des xénobiotiques. En conclusion, dans ce modèle, pour l'ensemble des paramètres explorés, sur le testicule, l'hypophyse, la prostate, le sang et le foie, nous n'avons observé que des effets à seuil et aucun effet non monotone.

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