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NRP Endocrine Disruptors

Intermediate Summary

Disruption of Glucocorticoid- and Mineralocorticoid Receptor-Mediated Responses by Environmental Chemicals

Project leader

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Environmental Chemicals Disrupt Corticosteroid Hormone Action

Enhanced glucocorticoid levels have been associated with several diseases, including type 2 diabetes, osteoporosis and cataracts. We found that dithiocarbamates and organotins, industrial chemicals, selectively and potently inhibited the enzyme controlling intracellular inactivation of glucocorticoids. In contrast, flavanones, natural compounds, inhibited glucocorticoid activation in intact cells.

Project description:

Research questions

The inappropriate action of cortisol induces an array of metabolic effects including osteoporosis, weight gain, loss of cognitive function, diabetes, and cataracts, whereas increased levels of the hormone aldosterone cause renal salt retention with hypertension, hypokalemia and heart failure. We investigated whether environmental chemicals exist that lead to the disruption of aldosterone (mineralocorticoid) and cortisol (glucocorticoid) hormone action. A series of relevant compounds was tested for effects on mineralocorticoid- and glucocorticoid receptor and, in addition, on 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1), which converts inactive glucocorticoids into their active forms and type 2 (11 β -HSD2), which catalyzes the reverse reaction.

Results

We identified, among others, two classes of chemicals that selectively disrupt the local inactivation of glucocorticoids by 11 β -HSD2. The inhibition of 11 β -HSD2 by dithiocarbamates was irreversible, whereas that by organotins was reversible. The reducing agent dithiothreitol (a dithiol compound) protected 11 β -HSD2 from inactivation by both classes of chemicals. The endogenous reducing agent glutathione (a monothiol compound) was able to prevent dithiocarbamate-induced inhibition but not that by organotins, indicating different mechanisms of inhibition of these two chemicals. Increased glucocorticoid action due to inhibition of 11 β -HSD2 may contribute to the toxicity of these chemicals.

Flavanone and some hydroxylated derivatives, but not flavones, selectively inhibited 11 β -HSD1 and were able to reduce glucocorticoid activation in liver cells and in adipose cells.

We also described a novel function of 11 β -HSD1 by catalyzing the oxoreduction of 7-ketocholesterol, the major oxidation product upon processing cholesterol-rich food. Thus, 11 β -HSD1 has an important role in the local activation of glucocorticoids, which at excessive levels are associated with metabolic disorders. We provide evidence that 11 β -HSD1 has also an important role in the detoxification of carbonyl compounds, including 7-ketocholesterol.

Perspectives

Our studies demonstrate that relevant environmental chemicals exist that interfere with glucocorticoid and mineralocorticoid hormone action. The age-dependent increasing frequency and accumulation of inappropriate aldosterone and cortisol action, due to receptor response modulation by endocrine disruptor compounds during life, might contribute to several pathological processes, including developmental disorders, osteoporosis, cataracts, cardiovascular disease and type 2 diabetes.