II CONGRESO INTERNACIONAL DE PSICOBIOLOGÍA

2nd INTERNATIONAL CONGRESS OF PSYCHOBIOLOGY

ÁVILA, SPAIN

July, 2017

ABSTRACT BOOK

Thursday 20th **Plenary Lecture 2**

ENVIRONMENTAL MODULATION OF NEURAL CIRCUITS: HOW GENISTEIN OR OTHER ENDOCRINE DISRUPTORS MAY INTERFERE WITH THE NEUROENDOCRINE BRAIN AND RELATED BEHAVIORS

GianCarlo Panzica, Marilena Marraudino, Alice Farinetti, Giovanna Ponti, Stefano Gotti

Department of Neuroscience, University of Torino, Italy and Neuroscience Institute Cavalieri Ottolenghi (NICO), Orbassano

Steroid hormones, in particular estrogens, are among the most important factors to regulate the development of the central nervous system (CNS). In fact, they may regulate neurogenesis, process outgrowth and synaptogenesis, concurring in this way to the development of specific pathways and functions. In many cases these functions as well as the neural pathways are sexually dimorphic and steroid sensitive also in the adulthood.

In the last 30 years, it has been progressively discovered in the environment that several substances of synthetic or natural origin may bind to hormone receptors. These substances are now called endocrine disrupting chemicals (EDCs) and may impact all those organs having hormonal receptors, including the brain. Many EDCs bind to steroid hormone receptors and this may impact brain and behavior differentiation.

Our and other data, collected in the last 10 years, demonstrate that the effects of EDCs on the brain are dependent by the age, the sex, and the region. The analysis of these effects is therefore not simple. In addition, the effects of a particular EDC will vary over the lifecycle of the animal and exposure during embryonic development may have short and/or long-term consequences. EDCs may permanently alter neural circuits and physiological properties, including the behavior. These effects may take place at dosis that are considered no effect by the actual legislation.

In our studies we tested the effects of several EDCs during the embryonic development of birds or during pregnancy and early postnatal period in mice. In both models we observed gender-oriented alterations of sexually dimorphic circuits and behaviors. Our data suggest that precocious exposure to EDCs through maternal administration (in mamamls) or in egg deposition (in birds) may permanently alter some sexually dimorphic circuits and influence in a gender-oriented way some behaviors. In particular, the timing of exposure to EDCs is a critical factor, such that the effects of a particular EDC will vary over the lifecycle of the animal as well as across species and phyla. Therefore, exposure to the estrogenic chemicals during embryonic development has consequences beyond impaired function of the reproductive axis. This makes it very challenging to evaluate the short and long-term effects of EDCs.

Many EDCs are of synthetic origin (i.e Bisphenol A, DDT and its derivatives, trybutiltin, phthalates and others), however some bioactive natural compounds (nutraceuticals) may act as EDCs and interfere with the neuroendocrine circuits. Isoflavones are an important group of nutraceuticals highly present in many animal feed and nutritional supplements which are soy based, being this plant an important source of proteins. Among the isoflavones present in soy, genistein is one of the most interesting molecules. It has an estrogenic effect which may interfere with hypothalamic circuits in different ways. The use of soy based formulas for neonates has increased in the recent

years. Different studies explored the effects of genistein in human infants, and in rodents but its long-term effects are still poorly understood. In our experimental models, pre- or post-natal exposure to genistein induced alteration of both behavior and neural circuits, and in many cases the effects were also sexually dimorphic.

Due to the large presence of EDCs in the environment and the food, as well as to their peculiar action during the brain differentiation, it seems reasonable that these compounds may concur to the development of some neural diseases that depends by alterations of brain circuits that are influenced by hormones during their normal development. In particular, due to the large number of EDCs that may bind to sex hormones' receptors, all neurological diseases that show a sex-ratio different from 1:1 are potentially affected by EDCs.

Therefore, exposure to the EDCs during embryonic development has consequences beyond impaired function of some neuroendocrine circuits. This makes it very challenging to evaluate their short and long-term effects. These compounds are therefore a third player within the nervous system and the evolutionary implications of having them in the normal food supply for certain human populations (i.e. phytoestrogen derivatives from soy), as well as for wild and farm animals should stimulate a wide discussion about their beneficial or adverse role.

References

1. Bo E, Farinetti A, Marraudino M, Sterchele D, Eva C, Gotti S, Panzica GC. Adult exposure to tributyltin affects hypothalamic neuropeptide Y, Y1 receptor distribution, and circulating leptin in mice. *Andrology*. 2016; **4**: 723-34.
2. Frye C, Bo E, Calamandrei G, Calza L, Dessi-Fulgheri F, Fernandez M, Fusani L, Kah O, Kajta M, Le Page Y, Patisaul HB, Venerosi A, Wojtowicz AK, Panzica GC. Endocrine Disrupters: A Review of Some Sources, Effects, and Mechanisms of Actions on Behaviour and Neuroendocrine Systems. *J Neuroendocrinol*. 2012; **24**: 144-59.
3. Gotti S, Martini M, Viglietti-Panzica C, Miceli D, Panzica GC. Effects of estrous cycle and xenoestrogens expositions on mice nitric oxide producing system. *Ital J Anat Embryol*. 2010; **115**: 103-8.
4. Heindel JJ, Blumberg B, Cave M, Machtinger R, Mantovani A, Mendez MA, Nadal A, Palanza P, Panzica G, Sargis R, Vandenberg LN, Vom Saal F. Metabolism disrupting chemicals and metabolic disorders. *Reprod Toxicol*. 2017; **68**: 3-33.
5. Martini M, Miceli D, Gotti S, Viglietti-Panzica C, Fissore E, Palanza P, Panzica GC. Effects of perinatal administration of bisphenol A on the neuronal nitric oxide synthase expressing system in the hypothalamus and limbic system of CD1 mice. *J Neuroendocrinol*. 2010; **22**: 1004-12.
6. Mura E, Barale C, Quinn Jr MJ, Panzica GC, Ottinger MA, Viglietti Panzica C. Organizational Effects of DDE on Brain Vasotocin System in Male Japanese Quail. *Neurotoxicology*. 2009; **30**: 479-84.
7. Ottinger MA, Lavoie E, Thompson N, Barton A, Whitehouse K, Abdelnabi M, Quinn MJ, Jr., Panzica GC, Viglietti-Panzica C. Neuroendocrine and Behavioral Effects of Embryonic Exposure to Endocrine Disrupting Chemicals in Birds. *Brain Res Rev*. 2008; **57**: 376-85.
8. Panzica GC, Viglietti Panzica C, Ottinger MA. Neurobiological impact of environmental estrogens. *Brain Res Bull*. 2005; **65**: 187-91.
9. Panzica GC, Viglietti-Panzica C, Mura E, Quinn Jr MJ, Palanza P, Ottinger MA. Effects of xenoestrogens on the differentiation of behaviorally relevant neural circuits. *Front Neuroendocrinol*. 2007; **28**: 179-200.
10. Panzica GC, Mura E, Miceli D, Martini M, Gotti S, Viglietti Panzica C. Effects of xenoestrogens on the differentiation of behaviorally-relevant neural circuits in higher
11. vertebrates. In: Vaudry H, Rubois E, Coast GM, Vallarino M, eds. *Trends in Comparative Endocrinology and Neurobiology*. New York, NY: New York Academy of Sciences 2009: 271-8.
12. Panzica GC, Bo E, Martini MA, Miceli D, Mura E, Viglietti-Panzica C, Gotti S. Neuropeptides and Enzymes are Targets for the Action of Endocrine Disrupting Chemicals in the Vertebrate Brain. *J Toxicol Environ Health B Crit Rev*. 2011; **14**: 449-72.
13. Panzica G, Melcangi RC. Structural and molecular brain sexual differences: A tool to understand sex differences in health and disease. *Neurosci Biobehav Rev*. 2016; **67**: 2-8.
14. Ponti G, Rodriguez-Gomez A, Farinetti A, Marraudino M, Filice F, Foglio B, Sciacca G, Panzica GC, Gotti S. Early postnatal genistein administration permanently affects nitrergic and vasopressinergic systems in a sex-specific way. *Neuroscience*. 2017; **346**: 203-15.
15. Rodriguez-Gomez A, Filice F, Gotti S, Panzica G. Perinatal exposure to genistein affects the normal development of anxiety and aggressive behaviors and nitric oxide system in CD1 male mice. *Physiol Behav*. 2014; **133**: 107-14.
16. Slama R, Bourguignon JP, Demeneix B, Ivell R, Panzica G, Kortenkamp A, Zoeller T. Scientific Issues Relevant to Setting Regulatory Criteria to Identify Endocrine Disrupting Substances in the European Union. *Environ Health Perspect*. 2016; **124**: 1497-503.
17. Viglietti-Panzica C, Montoncello B, Mura E, Pessatti M, Panzica GC. Organizational effects of diethylstilbestrol on brain vasotocin and sexual behavior in male quail. *Brain Res Bull*. 2005; **65**: 225-33.
18. Viglietti-Panzica C, Mura E, Panzica GC. Effects of early embryonic exposure to genistein on male copulatory behavior and vasotocin system of Japanese quail. *Horm Behav*. 2007; **51**: 355-63.


UNED
Facultad
de Psicología
Departamento de Psicobiología


Ayuntamiento
de Ávila
Del Rey · De los Leales · De los Caballeros


Diputación de Ávila
FUNDACIÓN CULTURAL
SANTA TERESA


EDITORIAL
sanz y torres
BIBLIOGRAFÍAS RECOMENDADAS · TEXTOS U.N.E.D.


aulamédica
formación en salud
www.aulamedica.es
40 años de Salud
1977-2017


EDITORIAL MEDICA
panamericana