STRESS AND EPIGENETIC

DR JOSE ARTURO VELA STAINES

IMPORTANCIA DE LAS PRIMERAS SEÑALES DE AUTISMO

- El autismo es un trastorno neurológico complejo que generalmente dura toda la vida
- La persona con autismo tiene afectada la capacidad para comunicarse y relacionarse con otros. También, está asociado con rutinas y comportamientos repetitivos, tales como arreglar objetos obsesivamente o seguir rutinas muy específicas. Los síntomas pueden oscilar desde leves hasta muy severos.
- En particular: Area socio emocional, habilidades para comunicarse e intereses restringidos y repetitivos

IMPORTANCIA DE LAS PRIMERAS SEÑALES DE AUTISMO

Actualmente se diagnostica con autismo a 1 de cada 68 individuos y a 1 de cada 42 niños varones, haciéndolo más común que los casos de cáncer, diabetes y SIDA pediátricos combinados.

El abordaje terapéutico

- Los tratamientos intensivos para los síntomas centrales del autismo responden a los temas de:
  - Socialización
  - Comunicación y cognición (ABA y Floor Time)
  - Alergias, intolerancias a ciertos alimentos, problemas gastrointestinales o trastornos del sueño, estos síntomas deben ser tratados también.

- A person with ASD might:
- Not respond to their name by 12 months of age
- Not point at objects to show interest (point at an airplane flying over) by 14 months
- Not play "pretend" games (pretend to "feed" a doll) by 18 months
- Avoid eye contact and want to be alone
- Have trouble understanding other people's feelings or talking about their own feelings
- Have delayed speech and language skills
- Repeat words or phrases over and over (echolalia)

La persona

- Sujeto portador de naturaleza racional:
- La persona desde que está in útero es capaz de sentir, no sabemos el momento en que inicia la subconciencia
- Tiene afectos, es capaz de comunicarse
- Merece todo nuestro respeto y admiración
- Es deber de los cuidadores de la salud ayudar en lo que sea posible para disminuir el stress materno

La neurobiología del apego y la Constitución del cerebro materno

- http://developingchild.harvard.edu/index.php/resources/multimedia/videos/three_core_concepts/

- La importancia del desarrollo del ser humano in utero y en los primeros años de vida.
- Como afecta el comportamiento que se tiene sobre la madre y sobre el bebe.
- O como afecta el estrés materno-fetal y del niño desde su nacimiento y los primeros años de vida
- Como afectan los Agentes químicos y el tipo de alimentación.
- El resultado es que algunos genes se apagan o prenden, pudiendo descarrilar la arquitectura cerebral del bebe

National Scientific Council on the Developing Child: Early experiences can alter gene expression and affect long term Development: wp 10

New scientific research shows that environmental influences can actually affect

Whether and how genes are expressed. Thus, the old ideas that genes are **"set in stone"** or that they alone determine development have been disproven. In fact, scientists have discovered that early experiences can determine how genes are turned on and off and even whether some are expressed at all.

Therefore, ***the experiences children have early in life—and the environments in which they have them—shape their developing brain architecture and strongly affect whether they grow up to be healthy, productive members of society. This growing scientific evidence supports the need for society to re-examine the way it thinks about the circumstances and experiences to which young children are exposed.***

National Scientific Council on the Developing Child: Early experiences can alter gene expression and affect long term Development: wp 10

- Nuevas investigaciones científicas muestran que las influencias ambientales pueden afectar el hecho de si y cómo se expresan los genes.
- Por lo tanto, las viejas ideas que los genes son ”inamovibles" o que son la llave que determina el desarrollo han sido desaprobadas.
- De hecho, los científicos han descubierto que las experiencias tempranas pueden determinar qué genes se activan y desactivan.

National Scientific Council on the Developing Child: Early experiences can alter gene expression and affect long term Development: wp 10

- Por lo tanto, las experiencias que tienen los niños en el período inicial de la vida-así como los ambientes en que viven en le dan forma a la arquitectura de su cerebro en desarrollo y afectan fuertemente para ser sanos y productivos miembros de la sociedad.
- La creciente evidencia científica apoya la necesidad de que la sociedad vuelva a examinar la forma en que piensa acerca de las circunstancias y experiencias a las que los jóvenes están expuestos desde niños.

- Los aproximadamente 23000 genes que los niños heredan de sus padres forman la llamada “Estructura Genómica”
- Comparando la estructura del genoma al Hardware de la computadora – ambos determinarán los limites de lo que es posible pero no trabaja sin un sistema operativo que le dice que es lo que hay que hacer
- ***En el genoma el sistema operativo es llamado “Epigenoma” Como el software en un sistema operativo, el epigenoma determina cuales funciones el hardware genetico hará o no***

Este sistema es construido con el tiempo como: experiencias positivas, como la exposición a oportunidades de aprendizaje positivos o influencias negativas como toxinas ambientales o una vida de circunstancias estresantes, están dejan una impresión química en los genes estas impresiones pueden ser temporales o permanentes y ambos muestran como los genes se apagan o se prenden

- El campo de la epigenetica es relativamente nuevo y esta a la vanguardia de las ciencias biologicas

- Ciertas experiencias pueden tambien causar modificaciones epigenéticas duraderas en cientos de genes que han sido ya identificados y la lista continua creciendo

NATIONAL SCIENTIFIC COUNCIL ON THE DEVELOPING CHILD

Early Experiences Can Alter Gene Expression and Affect Long-Term Development

WORKING PAPER 10

Center on the Developing Child HARVARD UNIVERSITY

How Early Experiences Alter Gene Expression and Shape Development

- Repitiendo, experiencias altamente estresantes podrán causar cambios epigenéticos que dañan los sistemas que administrarán las respuestas a situaciones adversas a lo largo de la vida

- La ciencia nos dice que la firma quimica impresa en nuestros genes en el desarrollo infantil y fetal pueden tener una influencia importante en la arquitectura cerebral que dura toda la vida. Para decirlo en pocas palabras, el descubrimiento del epigenoma proporciona una explicación, a nivel molecular, de por qué y cómo las primeras experiencias positivas y negativas pueden tener un impacto permanente.

nature neuroscience

Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse

Patrick O McGowan[1,2], Aya Sasaki[1,2], Ana C D'Alessio[3], Sergiy Dymov[3], Benoit Labonté[1,4], Moshe Szyf[2,3], Gustavo Turecki[1,4] & Michael J Meaney[1,2,5]

Maternal care influences hypothalamic-pituitary-adrenal (HPA) function in the rat through epigenetic programming of glucocorticoid receptor expression. In humans, childhood abuse alters HPA stress responses and increases the risk of suicide. We examined epigenetic differences in a neuron-specific glucocorticoid receptor (*NR3C1*) promoter between postmortem hippocampus obtained from suicide victims with a history of childhood abuse and those from either suicide victims with no childhood abuse or controls. We found decreased levels of glucocorticoid receptor mRNA, as well as mRNA transcripts bearing the glucocorticoid receptor 1_F splice variant and increased cytosine methylation of an *NR3C1* promoter. Patch-methylated *NR3C1* promoter constructs that mimicked the methylation state in samples from abused suicide victims showed decreased NGFI-A transcription factor binding and NGFI-A–inducible gene transcription. These findings translate previous results from rat to humans and suggest a common effect of parental care on the epigenetic regulation of hippocampal glucocorticoid receptor expression.

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There are maternal effects on the development of individual differences in behavioral and HPA stress responses in rodents and nonhuman primates[1,2]. Maternal behavior alters the development of HPA responses to stress in the rat through tissue-specific effects on gene transcription[3,4], including forebrain glucocorticoid receptor expression, the activation of which inhibits HPA activity through negative-feedback inhibition[5]. Thus, selective knockdown of glucocorticoid receptor expression in the corticolimbic system in rodents is associated with increased HPA activity under both basal and stressful conditions[6,7]. Conversely, glucocorticoid receptor overexpression is associated with a dampened HPA stress response[8].

Familial function and childhood adversity are linked to altered HPA stress responses in humans, which are associated with an increased risk for multiple forms of psychopathology[9–11]. There is evidence for decreased hippocampal glucocorticoid receptor expression in several psychopathological conditions associated with suicide, including schizophrenia and mood disorders[12–14]. Suicide is also strongly associated with a history of childhood abuse and neglect, and this effect is independent of that associated with psychopathology[15,16]. Thus, environmental events that associate with decreased hippocampal glucocorticoid receptor expression and increased HPA activity enhance the risk of suicide.

The effects of maternal care on hippocampal glucocorticoid receptor expression, and therefore HPA responses to stress, in the adult rodent are associated with an epigenetic modification of a neuron-specific exon 1_7 glucocorticoid receptor (*Nr3c1*) promoter[4,17]. We attempted to translate these findings to humans. We examined glucocorticoid receptor expression and *NR3C1* promoter methylation in hippocampal samples obtained from suicide victims and control subjects who died suddenly of unrelated causes. The focus of our examination was the *NR3C1* (also known as $GR1_F$) promoter, the homolog of the exon 1_7 region in the rat[18], which is highly expressed in human hippocampus[19]. Suicide victims were either positive or negative for history of childhood abuse (sexual contact, severe physical abuse and/or severe neglect), allowing for the separation of the effects associated with childhood abuse from those associated with suicide *per se*. Our controls were all negative for a history of childhood abuse.

RESULTS

Hippocampal glucocorticoid receptor expression

The human glucocorticoid receptor gene *NR3C1* covers a region of more than 80 kb in chromosome 5, containing eight coding exons (exons 2–9) and alternative 5′ noncoding exon 1s[19–21]. The 5′ untranslated region (UTR) of exon 1 of the *NR3C1* gene determines the tissue-specific expression. The 5′ UTR of *NR3C1* contains 11 exon 1 splice variants, all of which bear unique splice donor sites and share a common exon 2 splice acceptor site[19]. Exon 1_F of *NR3C1* is similar to the rat exon 1_7, which reveals a maternal effect on cytosine methylation and expression[8,18,22]. Because individuals with severe forms of major depression show decreased glucocorticoid receptor

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ORIGINAL ARTICLE

Elevated fetal steroidogenic activity in autism

S Baron-Cohen[1,10], B Auyeung[1,2], B Nørgaard-Pedersen[3], DM Hougaard[3], MW Abdallah[3,4,5], L Melgaard[3], AS Cohen[3], B Chakrabarti[1,6], L Ruta[1,7] and MV Lombardo[1,8,9,10]

Autism affects males more than females, giving rise to the idea that the influence of steroid hormones on early fetal brain development may be one important early biological risk factor. Utilizing the Danish Historic Birth Cohort and Danish Psychiatric Central Register, we identified all amniotic fluid samples of males born between 1993 and 1999 who later received ICD-10 (International Classification of Diseases, 10th Revision) diagnoses of autism, Asperger syndrome or PDD-NOS (pervasive developmental disorder not otherwise specified) ($n = 128$) compared with matched typically developing controls. Concentration levels of Δ4 sex steroids (progesterone, 17α-hydroxy-progesterone, androstenedione and testosterone) and cortisol were measured with liquid chromatography tandem mass spectrometry. All hormones were positively associated with each other and principal component analysis confirmed that one generalized latent steroidogenic factor was driving much of the variation in the data. The autism group showed elevations across all hormones on this latent generalized steroidogenic factor (Cohen's $d = 0.37$, $P = 0.0009$) and this elevation was uniform across ICD-10 diagnostic label. These results provide the first direct evidence of elevated fetal steroidogenic activity in autism. Such elevations may be important as epigenetic fetal programming mechanisms and may interact with other important pathophysiological factors in autism.

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INTRODUCTION

Autism is characterized by early developmental difficulties in social interaction and communication, alongside highly repetitive stereotyped behavior and/or restricted interests. It affects approximately 1% of the population, and males are diagnosed more often than females.[1] While changing diagnostic practice over time and other social variables likely partly contribute to this male bias, biological factors related to the sex chromosomes and/or fetal sex steroids may also have important roles.[2,3] Given their capacity to exert epigenetic fetal programming influence during early critical periods of brain development,[4–7] steroid hormones are well-positioned as an important early fetal environmental factor that may interact with other risk factors for autism and other atypical neurodevelopmental conditions that asymmetrically affect the sexes.[2,8–11]

Prior work has shown that one prominent sex steroid, testosterone, has wide-ranging influence on phenotypic variability related to autism. For example, fetal testosterone influences individual differences in typical development in eye contact, vocabulary size, restricted interests, mentalizing, empathy, systemizing, attention to detail and autistic traits.[11] Emerging neuroimaging evidence also supports a role for fetal testosterone affecting individual differences in structural and functional brain development in directions congruent with patterns of sexual dimorphism, and in brain regions known to develop atypically in autism and other sex-biased developmental psychopathologic conditions.[2,9,12]

The 'extreme male brain' theory of autism,[3] which is primarily an account about the cognitive phenotype of autism, makes mechanistic predictions about the role of elevated fetal sex steroids such as testosterone in the development of autism. However, the extreme male brain theory does not exclude the role of other mechanisms such as the role of sex chromosome effects or the role of other steroid hormones proximal to testosterone in biosynthesis pathways (e.g., estradiol, progesterone and cortisol). Therefore, although prior work in relation to autism has mainly tested fetal testosterone, it may be that the actions of testosterone and other precursor steroid hormones within the same biosynthesis pathway (e.g., the Δ4 sex steroid pathway) all have significant roles during fetal development in autism. For example, prior genetic association evidence has found a role for cytochrome *P*450-containing enzymes in autism (e.g., CYP17A1, CYP19A1 and CYP11B1).[13] These enzymes are critical for the conversion of different hormones along the Δ4 pathway that lead up to testosterone (e.g., progesterone, 17α-hydroxy-progesterone and androstenedione) as well as for conversion of Δ4 steroids such as progesterone and 17α-hydroxy-progesterone toward cortisol (see Supplementary Figure 1). Thus, in this study we test the role of not only fetal testosterone but also precursor steroids within the Δ4 pathway, as well as the non-Δ4 steroid hormone cortisol, as potential mechanisms that are elevated during fetal development in autism.

[1]Autism Research Centre, Department of Psychiatry, University of Cambridge, Cambridge, UK; [2]Department of Psychology, University of Edinburgh, Edinburgh, UK; [3]Department of Clinical Biochemistry and Immunology, Statens Serum Institute Copenhagen, Copenhagen, Denmark; [4]Department of Child and Adolescent Neuropsychiatry, Rostock University Medical Centre, Rostock, Germany; [5]Section for Epidemiology, Department of Public Health, Aarhus University, Aarhus, Denmark; [6]Centre for Integrative Neuroscience and Neurodynamics, School of Psychology and Clinical Language Sciences, University of Reading, Reading, UK; [7]Division of Child Neurology and Psychiatry, Stella Maris Scientific Institute, Pisa, Italy; [8]Department of Psychology, University of Cyprus, Nicosia, Cyprus and [9]Centre for Applied Neuroscience, University of Cyprus, Nicosia, Cyprus. Correspondence: Professor S Baron-Cohen, Autism Research Centre, Department of Psychiatry, University of Cambridge, Douglas House, 18B Trumpington Road, Cambridge CB2 8AH, UK.
E-mail: sb205@cam.ac.uk
[10]These authors contributed equally to this work.
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Enhanced Cortisol Response to Stress in Children in Autism

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Abstract

Children with Autism often show difficulties in adapting to change. Previous studies of cortisol, a neurobiologic stress hormone reflecting hypothalamic–pituitary–adrenal (HPA) axis activity, in children with autism have demonstrated variable results. This study measured cortisol levels in children with and without Autism: (1) at rest; (2) in a novel environment; and (3) in response to a blood draw stressor. A significantly higher serum cortisol response was found in the group of children with autism. Analysis showed significantly higher peak cortisol levels and prolonged duration and recovery of cortisol elevation following the blood-stick stressor in children with autism. This study suggests increased reactivity of the HPA axis to stress and novel stimuli in children with autism.

- Por otro lado ambientes enriquecedores de apoyo y aprendizaje generan impresiones positivas epigenéticas que activan el potencial genético
- En este segundo caso, la estimualción que ocurre en el cerebro a traves del uso activo del aprendizaje y circuitos de memoria puede resultar en cambios epigenticos que establecen una fundación para mas efectivas capacidades de aprendizaje en un futuro

MAKERS OF MODERN PSYCHOTHERAPY
John Bowlby
& Attachment Theory
Jeremy Holmes

The expectant brain: adapting for motherhood

Paula J. Brunton & John A. Russell

Abstract | A successful pregnancy requires multiple adaptations of the mother's physiology to optimize fetal growth and development, to protect the fetus from adverse programming, to provide impetus for timely parturition and to ensure that adequate maternal care is provided after parturition. Many of these adaptations are organized by the mother's brain, predominantly through changes in neuroendocrine systems, and these changes are primarily driven by the hormones of pregnancy. By contrast, adaptations in the mother's brain during lactation are maintained by external stimuli from the young. The changes in pregnancy are not necessarily innocuous: they may predispose the mother to post-partum mood disorders.

The maternal brain is a major force in driving essential physiological changes during pregnancy. These changes include adaptations that cushion the impact on the fetus of the mother's experience of stress during the pregnancy, that reset the control of metabolism to favour energy flow to the fetus and that store energy as adipose tissue in preparation for lactation. The mother's brain also undergoes changes that prepare the neuroendocrine systems that regulate the pulsatile release of oxytocin secretion at parturition and during lactation, and that regulate the secretion of prolactin to ensure that milk is produced after birth[1].

A new mother displays a dramatic change in behaviour as soon as the babies are born: she immediately cares for the young and defends them. The expression of these essential components of maternal behaviour is the culmination of changes, controlled by pregnancy hormones, in the activity of neural circuitry in late pregnancy, but is held in check until the fetuses are delivered (again under the control of the pregnancy hormones). However, the changes in the brain that permit motherhood involve altered emotionality, and are not without cost. The sudden withdrawal of the pregnancy hormones before and at birth not only permits the activation of essential post-partum maternal behaviours and neuroendocrine functions for lactation, but may also predispose the new mother to depression.

Recently, major progress has been made in our understanding of the organization and molecular mechanisms of the neuroendocrine networks that govern mammalian parturition, lactation, maternal behaviour and maternal stress responsiveness. Understanding these processes might help improve the management of pregnancy to assist an optimal outcome for the infant, and might lead to an explanation of the mental health disturbances that often occur in women after even a successful pregnancy. Such knowledge might have wider implications for the development of new therapeutic approaches to mental ill-health.

This Review discusses the mechanisms that protect the fetus from maternal glucocorticoids and the adaptations in maternal neuroendocrine systems that are necessary for normal pregnancy, parturition and lactation. It then describes the adaptations in the brain that are required for maternal behaviour and successful rearing of the offspring. Finally, it considers the implications of these adaptations for post-partum mood disorders.

Laboratory of Neuroendocrinology, Centre for Integrative Physiology, University of Edinburgh, Hugh Robson Building, George Square, Edinburgh, EH8 9XD, Scotland, UK.
Correspondence to: J.A.R.
e-mail: J.A.Russell@ed.ac.uk
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Protecting the fetus

Exposure to stress or synthetic glucocorticoids during pregnancy can affect the development of physiological systems in the offspring, resulting in increased susceptibility to cardiovascular[2] and metabolic disease[3] and to affective disorders in adulthood[4]. This phenomenon has been termed 'fetal programming'. There are 'in-built' mechanisms that protect the fetus from this potentially detrimental programming. As a last line of defence, the placenta expresses 11β-hydroxysteroid dehydrogenase 2 (11βHSD2)[5], an enzyme that acts as a barrier that limits the exposure of the fetus to circulating maternal glucocorticoids by converting corticosterone to inert 11-dehydrocorticosterone; a first line of defence is provided by changes in the activity of the maternal hypothalamus–pituitary–adrenal (HPA) axis (BOX 1).

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- POLITICAS PUBLICAS

- Las autoridades pueden utilizar este conocimiento para ayudar a la toma de decisiones sobre la asignación de recursos para las intervenciones que afectan a las circunstancias de la vida de los niños y saber que las intervenciones eficaces pueden literalmente cambiar la forma en que trabajan los genes de los niños y por ello, tener efectos a largo plazo sobre su salud mental y física, el aprendizaje y la conducta. En este sentido, el epigenoma es el vínculo crucial entre entornos externos que conforman nuestras experiencias y los genes que guían nuestro desarrollo.

Propuestas finales

1. Ser facilitadores para disminuir el estrés materno, básico para el apego seguro cuando menos dentro del primer año de vida
2. Promover el contacto piel con piel de parte de la madre y del padre en el nacimiento
3. Extender la licencia por maternidad y aumentar los permisos por paternidad
4. Promover la estimulación temprana socio emocional y de comunicación entre los padres y el bebe o en su defecto con el tercer cuidador
5. Profesionalizar los servicios de guardería para disminuir al mínimo el estrés del bebe
6. Preparar de mejor forma a los profesionales de la educación para evitar medidas coercitivas y de bulling en la escuela

Coexpression Networks Implicate Human Midfetal Deep Cortical Projection Neurons in the Pathogenesis of Autism

A. Jeremy Willsey,[1,2] Stephan J. Sanders,[1,2] Mingfeng Li,[3,4] Shan Dong,[1,5] Andrew T. Tebbenkamp,[3,4] Rebecca A. Muhle,[1,4,6] Steven K. Reilly,[1] Leon Lin,[7] Sofia Fertuzinhos,[3,4] Jeremy A. Miller,[8] Michael T. Murtha,[9] Candace Bichsel,[3,4] Wei Niu,[1,4,6] Justin Cotney,[1] A. Gulhan Ercan-Sencicek,[6,9] Jake Gockley,[1] Abha R. Gupta,[6,10] Wenqi Han,[3,4] Xin He,[11] Ellen J. Hoffman,[6,9] Lambertus Klei,[12] Jing Lei,[13] Wenzhong Liu,[1] Li Liu,[13] Cong Lu,[13] Xuming Xu,[3,4] Ying Zhu,[3,4] Shrikant M. Mane,[14] Ed S. Lein,[8] Liping Wei,[5,15] James P. Noonan,[1,4] Kathryn Roeder,[11,13] Bernie Devlin,[12,*] Nenad Sestan,[3,4,*] and Matthew W. State[1,2,6,9,16,*]

[1]Department of Genetics, Yale School of Medicine, New Haven, CT 06510, USA
[2]Department of Psychiatry, University of California, San Francisco, San Francisco, CA 94143, USA
[3]Department of Neurobiology, Yale School of Medicine, New Haven, CT 06510, USA
[4]Kavli Institute for Neuroscience, Yale School of Medicine, New Haven, CT 06510, USA
[5]Center for Bioinformatics, State Key Laboratory of Protein and Plant Gene Research, School of Life Sciences, Peking University, Beijing 100871, China

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