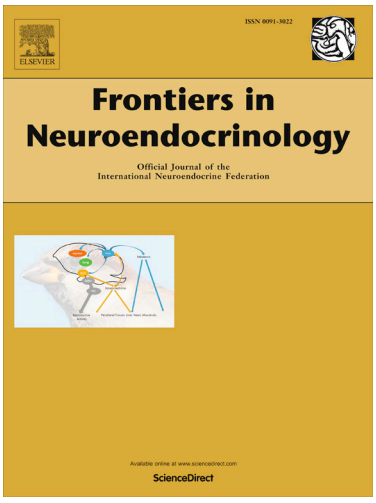
Accepted Manuscript



Review article

Impacts of Stress on Reproductive and Social Behaviors

A.M. Magariños, S.M. Schaafsma, D.W. Pfaff

PII: S0091-3022(18)30007-4
DOI: https://doi.org/10.1016/j.yfrne.2018.01.002
Reference: YFRNE 697

To appear in: *Frontiers in Neuroendocrinology*

Received Date: 17 July 2017
Revised Date: 19 January 2018
Accepted Date: 21 January 2018

Please cite this article as: A.M. Magariños, S.M. Schaafsma, D.W. Pfaff, Impacts of Stress on Reproductive and Social Behaviors, *Frontiers in Neuroendocrinology* (2018), doi: https://doi.org/10.1016/j.yfrne.2018.01.002

Frontiers in Neuroendocrinology-17-63 Revised

Impacts of Stress on Reproductive and Social Behaviors.

Magariños, A.M., Schaafsma. S.M. and D.W. Pfaff

Laboratory of Neurobiology and Behavior, The Rockefeller University, New York, NY

ABSTRACT: Impacts of steroid stress hormones on the brain have provided multiple opportunities for linking specific molecular phenomena to behavioral state. The negative impacts of stress on female reproductive biological processes have been documented thoroughly at the endocrine and behavioral levels. More recently, a '3-hit' theory of autism has identified early stress as one of the hits. The multiple biochemical effects of endotoxin (lipopolysaccharide, LPS) indicated that it would serve as a powerful maternal immune activator. The prenatal exposure to LPS coupled with the other two 'hits'- an autism-related mutation and the Y chromosome - - heightened certain autism-like signs in mouse behavior.

Keywords: Autism, hippocampus, stress, stress hormones, behavior.

Bruce McEwen's career in science has been remarkable in at least four of its aspects. First, his original research papers have been prolific and have had high impact in neuroendocrinology, specifically, and on neuroscience in general. Having published more than a thousand papers, he has covered a variety of stress-related subjects both during development and in the adult brain. For example, taking the phenomenon of postnatal neurogenesis in the dentate gyrus of the hippocampus (Altman, 1962), McEwen's lab showed, using immunocytochemistry, that both the glucocorticoid receptor and the mineralocorticoid receptor are expressed in newly born cells, and they inferred that expression of the glucocorticoid receptor affects cell survival (Gould et al., 1992a). Along the same lines, Gould et al (1992b) reported that numbers of newly divided 3H-thymidine-labeled nerve cells were significantly increased following adrenalectomy. Taking the two studies together, one concludes that stress hormones must oppose postnatal neurogenesis, a phenomenon whose behavioral consequences are still being worked out. With respect to adult hippocampal CA3 pyramidal neurons, chronic psychosocial stress alters the structure of axo-dendritic synapses, as studied by Golgi impregnation (Magariños et al, 1996) and at the ultrastructural level (Magariños et al, 1997). Further work with mice haploinsufficient in Brain Derived Neurotrophic Factor (BDNF) showed both the role of BDNF in supporting the formation of CA3 dendritic arbors and, in turn, the permissive role of BDNF in the effect of chronic restraint stress (Magariños et al., 2011).

Second, in terms of intellectual scope, McEwen has repeatedly exhibited intellectual command of his field. His New England Journal of Medicine review (1998) has been cited thousands of times. And his Physiological Reviews (2007) paper covered both the short-term

adaptive effects of stress hormone action in the brain and maladaptive effects of chronic stress. In fact, recently (McEwen, 2016 on Singletary, 2015) he has extended his thinking to include potential roles for allostatic load in the etiology of autism (also, see Schaafsma experiment, below).

Third, he has been willing to sacrifice his time in order to do service and provide leadership. In addition to serving on countless advisory groups, Bruce was President of the Society for Neuroscience, and at Rockefeller University he served as Associate Dean.

Fourth, over the decades, Bruce has repeatedly acted and written from a strong social conscience, which has led him, for example, to examine and warn about the enduring and harmful, stressful effects of substandard housing and environments.

Relating stress to social behaviors.

Here we review work showing how certain forms of stress can oppose reproductive and other social behaviors. These types of behaviors require optimal levels of CNS arousal, the relation of which to stress we have considered before (Pfaff et al, Stress, 2007). Hans Selye's (1946) initial 'alarm' stage of his General Adaptation Syndrome corresponds to what we have called 'generalized CNS arousal'. He defined the alarm reaction as "the sum of all non-specific phenomena elicited by sudden exposure to stimuli to which the organism is quantitatively or qualitatively not adapted" (p. 119). Both stress physiology and arousal physiology feature large numbers of specific agents causing a wide range of physiological effects, behavior and otherwise. However, there is an asymmetric relation between stress mechanisms and arousal mechanisms. Namely, all circumstances causing stress are theorized to cause arousal; but not all stimuli causing arousal are stressful.

The social behaviors considered here require high enough levels of arousal to enable the initiation of the appropriate responses (thus avoiding the stress of boredom), but low enough levels of arousal to avoid freezing up (thus avoiding the stress of excess demand).

One important form of social behavior is mating, which we consider in the next section.

Impacts of stress on female sex behaviors.

The causal routes by which reproductive mechanisms in the female can be inhibited by stress have been reviewed (Magarinos and Pfaff, 2016). The dynamics are interesting because, in terms of the specificity of neuroendocrine dynamics in space and time, the two families of phenomena, sex and stress, are the opposite of each other: Reproductive mechanisms from across the body and across the estrus cycle come together, focusing toward a short time interval

during which sex behavior occurs at about the time of ovulation. In a dramatic contrast, a stressful event in a single sensory modality at one specific time can have implications for physiology throughout the body, for a long time.

It is well known that stress interferes with the underlying processes of reproductive endocrinology in the female (Whirledge and Cidlowski, 2013), emphasizing, here, work with laboratory rodents. Less explored are the mechanisms by which stress can disrupt female sex behaviors. White and Uphouse (2004) used a stress that comprised 5 minutes of restraint with ovariectomized female rats primed with various doses of estradiol benzoate followed by 250 micrograms of progesterone. It had already been shown that females primed with estradiol (only) had their lordosis, a dorsiflexion of the vertebral column by which the female permits fertilization, reduced. In the new work she showed that priming doses of estradiol between 4 and 10 micrograms followed by 250 micrograms of progesterone prevented the lordosis-inhibiting effects of stress. In a later study (Uphouse and Hiegel, 2013) this team replicated the effect of stress, and then showed that the lordosis-protective effect of progesterone was itself blocked by a progesterone receptor antagonist CDB-4124. Thus, at least one form of stress reduces female reproductive behavior, and that stress effect is blocked by progesterone. This field of work needs to be expanded by the use of other forms of stress and additional means by which stress effects can be blocked.

One additional system through which stress effects on sex behaviors can be reduced would be the oxytocin/oxytocin receptor pathway, as theorized by McCarthy et al (1991). Clearly, oxytocin gene expression facilitates lordosis behavior (McCarthy et al, 1994), and this behavioral effect is ensured by progesterone actions in the ventromedial hypothalamus (Schulze and Gorzalka, 1991; Schumacher et al., 1990). Molecular steps would include the fact that estrogens increase gene expression for oxytocin (Chung et al 1991; Dellovade et al, 1999) and the oxytocin receptor (Schumacher et al, 1992; Quinones-Jenab et al, 1997), and, in turn, oxytocin increases lordosis. As part of this behavioral effect, oxytocin increases the firing rates of ventromedial hypothalamic neurons (Kow et al, 1991). Altogether, the steroid hormone progesterone and the neuropeptide oxytocin seem to cooperate in their protection against stress effects.

So far, this discussion has treated progesterone simply as the ligand of the progesterone receptor, acting through the cell nucleus. But 5-alpha reduced progesterone metabolites are powerful modulators of GABA-A receptors (Majewska, 1988; reviewed Schumacher et al., 2017; Brinton, 2013). The membrane-bound and cell nuclear mechanisms of progestin actions could conceivably cooperate, analogous to the two routes of estrogen actions on female reproductive behaviors (Kow and Pfaff, in Steroids, 2016a, b).

The next section relates stress to autism. If reproductive behaviors are, by necessity, the prototypical social behaviors among mammals, they nevertheless tend to be somewhat simpler

than the social behaviors whose problems trouble us in terms of medicine and public health. Social deficits comprise the key diagnostic item for autistic spectrum disorders (ASD).

Inclusion of stress in a 3-hit theory of autism.

In the face of overwhelming degrees of heterogeneity of symptoms and time courses of autism spectrum disorders, the one feature that seems to remain constant is the large sex difference: about 80% of the children diagnosed are boys. Years ago, working with the developmental psychologist Sylvie Goldman and the pediatric neurologist Isabelle Rapin, one of us devised a "3 hit" theory of autism, concentrating on the male predominance (Pfaff et al., 2011). This theory proposed that 3 types of factors would amplify each other's effects on the development of social behavior: prenatal stress, an autism-related genetic mutation, and having a Y chromosome (being male).

Early stress. Autism is now diagnosed in greater than 1 in 100 children, and because it begins so early in life and lasts into adulthood, it is occasioned by long-lasting emotional suffering and can entail enormous expenses for medical and psychological treatments. Sir Michael Rutter, who has participated in autism research for more than 40 years, has reviewed our current understanding of the genetic contributions to, and psychological treatments for ASDs (Rutter, 2011). For example, some decades ago, Folstein and Rutter (1977) reported 36% concordance of diagnoses of autism among monozygotic twins, compared with 0% in dizygotic twins, and in that paper anticipated the subsequent discussions of gene/environment interactions. Recently, in producing rigorous quantitative estimates of gene/environment contributions, Hallmayer et al (2011) estimated ASD diagnostic concordance rates at .77 for monozygotic male twins, with a large share (58%) of the variance in liability explained by environmental factors. He has proposed novel tests of the social problems focused on by our theory, including a theory-of-mind task (Heavey et al, 2000), and has explored the relationships between the dysphasia (i.e. severe language disorders) of autism and the evident shortcomings in social communication (Cantwell et al, 1989). For this review, it is important to illustrate how early stress plays into some of the multiple etiologies that lead to ASDs.

Evidence that early stress contributes to the development of autistic symptoms is overwhelming. The literature on animal research devoted to charting the behavioral consequences of early stress is more extensive than research with humans, and therefore will be covered first. Using Rhesus monkeys for animal studies potentially relevant to human behavioral development, Suomi and his colleagues (Dettmer et al, 2012) separated certain monkeys from their mothers, stressing them through either a peer-rearing paradigm (PR) or surrogate-peer-rearing (SPR) from birth through the first eight months of their lives. Control animals were reared by their mothers and peers (MPR). Most important for the present argument about the etiology of the social anxiety of autism, PR monkeys showed the greatest amount of

anxious behavior, and had high cortisol levels that remained high for months after the experiment. SPR animals also showed more anxiety than MPR animals. Subsequent work by Suomi and colleagues suggested abnormal regulation of serotonergic systems as having something to do with social withdrawal consequent to early psychosocial stress (Erickson et al, 2005).

Early stress can also affect the performance of a biologically crucial social behavior that some have considered prototypical for all social behaviors, namely, maternal behavior. Francis Champagne and her colleagues (2006) have imposed stress in the form of removing pregnant dams from their home cages and restraining them in small Plexiglas restrainers 3x30 minutes each day during the last 7 days of pregnancy, the timing distributed randomly throughout the day so that it could be considered unpredictable. They applied this procedure to female rats who naturally showed the highest levels of maternal behavior in the form of Licking and Grooming pups ('high LG') and also to females who showed the lowest levels ('low LG'). Pregnant females in the control group were left undisturbed. They found that while, as expected, high LG mothers showed more LG than low LG mothers toward the test litters, the stress protocol reduced LG performance in the high LG mothers to the point where those stressed females essentially were reduced to performing maternal behaviors at low LG levels. This striking action of stress carried over to females' behavior with the next litter produced by these females, a subsequent litter in which no new stress was applied. There was no effect of stress on low LG mothers, perhaps because of a 'floor effect'. Interestingly, group differences that looked parallel to these behavioral results were found when looking at binding of ligand to the oxytocin receptor (OTR) in limbic forebrain sites such as the central nucleus of the amygdala and the bed nucleus of the stria terminalis, as well as a forebrain region important for maternal behavior, the medial preoptic area. This result, coupled with behavioral tests in the open field, would suggest an effect of early stress to heighten some aspect of anxiety in these females, anxiety that normally would be reduced by OT acting at forebrain OTRs. Champagne (2010) envisions and produces evidence for the notion that early adversity affects behavior across the lifespan through epigenetic changes: long-lasting inheritable changes that do not involve alteration of DNA base sequences. While much evidence has implicated DNA methylation in such epigenetic phenomena (Weaver et al. 2004) other possibilities include the aceytlation and methylation of the tails of histone proteins, in chromatin, and the incursion of fragments of non-coding DNA. By no means were these studies intended to link maternal behavior to autism. Instead, findings from the Champagne and Meaney labs reveal molecular mechanisms by which early stress can lead to the alteration of a complete, biologically important, natural behavior.

New work. For the 3-hits which are theorized to multiply each other's' effects, we wanted a form of prenatal stress which is quantifiable. Maternal immune activation qualified, particularly since mothers' infections during pregnancy are known to predispose to autism (Atladóttir et al., 2010). Lipopolysaccharide (LPS) injections to the 7 day pregnant mouse,

intended to mimic a bacterial infection, was chosen as chemically cleaner than the Poly (I-C) method, intended to mimic a viral infection. The advantage of this choice has turned out to be that from batch to batch LPS has more constant biochemical properties than Poly (I-C). The surprising aspect of this choice was that we did not realize the powerful and widespread effects of LPS outside the brain (e.g. van der Poll and Lowry, 1996; Guerville and Boudry, 2016) and inside the brain (Schreuder et al, 2017). These include increases in plasma interleukin-10, tumor necrosis factor, fever, leukocytosis, neutrodegranulation, and the release of interleukins 6 and 8.

In the recent paper (Schaafsma et al., 2017), testing the '3 hit hypothesis' required measuring the synergistic effects of stress **X** ASD-related genetic mutation (contactin-associated protein-like 2, Cntnap2, knockout) **X** having a Y chromosome. In the results that were predicted by the 3-hit hypothesis, we investigated social communication by means of the number of vocalizations during a 5 minute maternal separation paradigm. Both male and female pups typically emit these calls, which elicit maternal retrieval of the pups. We found a significant effect of number of 'hits' the animals were exposed to on the number of vocalizations on postnatal day (PD) 3, the day featuring the highest amount of calling. That is, zero-hit pups showed the highest amount of vocal communication, and there was a monotonic decrease in the amount as one looked at the results from zero to 1 to 2 to 3 hits. Another assay whose results fitted the 3-hit theory very well was the test of social recognition, assays being performed on immediately post pubertal mice (postnatal day 40-42). Compared to the zero-hit mice, the 3-hit (a) showed less social interest to begin with; (b) showed less habituation to repeated intrusions by the same stimulus mouse; and (c) less reactivation of social approach upon intrusion by a new, unfamiliar stimulus mouse. These results emphasized the cumulative, 'multiplicative' nature of the 3 hits as only when the 3 hits are combined do we consistently see significant deficits across behavioral and molecular measures.

On the other hand, a different test of social approach, the traditional 3-chamber assay, did not show significant group differences. This may reflect the sensitivity of social behavior results to the conditions of the assay.

As well, the open field test yielded small but significant differences, but it was hard to see that these differences confirmed the 3-hit theory. That is, because ASD symptoms often co-occur with hyperactivity and anxiety, and to investigate whether increased activity or anxiety could account for the differences observed in the social-recognition test, we measured hyperactivity and anxiety in an open-field apparatus. We found that there are significant differences between groups in the distance traveled during the 10 min of free exploration in the open-field arena. The three-hit mice covered greater distance than the zero-hit and the one-hit mice. The two-hit mice covered more distance than the one-hit mice. No significant differences were found in time spent in the middle of the apparatus, a measure for anxiety. Looking at the individual hits, we found that only genotype resulted in significant differences, with WT mice covering less distance and spending less time in the middle of the apparatus than KO mice.

The same mice used in behavioral tests were also used for assays of mRNA levels and for epigenetic measurements, namely protranscriptional and transcription-repressive histone modifications. First we assayed for stress-related gene expression in limbic structures. The most significant result was in mRNA levels for CRH-R1 in the hippocampus. Surprisingly, this results was in the left hippocampus, but not the right hippocampus. No effects were found on CRH-BP or CRH-R2 expression.

Regarding histone N-terminus modifications**,** these can be induced in the hippocampus by experimental stress imposition (Hunter et al., 2009, 2012, 2015). For potential explanations of the mRNA data we used chromatin immunoprecipitation and studied a CRH-R1 promoter region that is very likely to include transcription factor binding sites for testis-determining SRY, as well as for the cellular stress-related signal NFKB1. That is, for potential explanations of the mRNA data, we studied alterations of lysine modifications on the histone H3 N terminus, as well as global acetylation levels of H3 over the Crhr1 promoter. We chose a primer pair that amplifies a genomic region −560 to −461 bp relative to Crhr1's transcriptional start site, which contains the promoter area that, according to TFSEARCH prediction (www.cbrc.jp/), is very likely to include transcription factor binding sites for testis-determining SRY, as well as for the cellular stress-related signal NF-κB1, and may therefore be especially important in the underlying mechanisms of sex-specific effects of gene–environment interactions. These two DNA binding processes would reflect 2 of the 3 'hits'. The overall pattern of results for two protranscriptional histone modifications, histone 3 (H3) trimethylation on lysine 4 (H3K4me3) and H3 acetylation fit what would be predicted by the 3-hit theory in that DNA binding was numerically greater for the zero hit than for the 3-hit condition. However, the same pattern across experimental groups also obtained for H3K27me3, a repressive mark. Our theory would not predict that result.

On the one hand, this study provided evidence for one causal route leading to the male predominance in diagnoses of autism. But there are four caveats. (i.) It is likely one causal route out of many, the others being, as of now, unknown. (ii.) The LPS maternal immune activation appears to be a more devastating stress manipulation, bodywide, than we expected. (iii.) Regarding the relative numbers of boy and girl patients, there could be some diagnosis bias. (iv.) While we began the study thinking of early androgenic hormone effects on the brain as contributing to the large sex difference in autism, there are at least three other potential mechanisms (Arnold, 2012; Schaafsma and Pfaff, 2014). Other sets of mechanisms include direct effects of various Y-linked genes, skewed X-inactivation, parent-of-origin imprinting of specific gene alleles and the possibility of the inactivated X chromosome as a heterochromatin sink for chromatin proteins. Thus, regarding the sex difference in autism there remains a lot of work to be done.

Implications.

Regarding potential implications of these data in laboratory animals for human social behavior, two points can be made. First, in terms of social behavior in general, there is little

question that stress can have an important role (reviewed, Caldwell et al., 2017; Farah, 2017). But, second, the argument has been made by developmental psychologists that the sex difference in autism diagnoses does not depend solely on the mechanisms discussed above, but instead that diagnosis bias also plays a role (Goldman, 2013).

Acknowledgements.

Funded by the Simons Foundation and the New York Neuroscience Foundation

References

Altman J (1962) Are new neurons formed in the brains of adult mammals? Science 135: 1127-1128.

Arnold, AP (2012) The end of gonad-centric sex determination in mammals. Trends in Genetics 28:55-61.

Atladóttir HO, Thorsen P, Østergaard L, Schendel DE, Lemcke S, Abdallah M, Parner ET (2010) Maternal infection requiring hospitalization during pregnancy and autism spectrum disorders. J Autism Dev Dis 40:1423-1430.

Brinton RD (2013) Neurosteroids as regenerative agents in the brain: therapeutic implications Nat Rev Endocrinol 9: 241-250.

Caldwell HK, Aulino, EA, Rodriguez KM, Witchey SK and Yaw AM (2017) Social context, stress, neuropsychiatric disorders, and the vasopressin 1b receptor Front Neurosci 11(OCT):567.

Cantwell DP, Baker L, Rutter M, Mawhood L. Infantile autism and developmental receptive dysphasia: a comparative follow-up into middle childhood. J Autism Dev Disord. 1989 19(1):19-31.

Champagne FA, Meaney MJ. (2006) Stress during gestation alters postpartum maternal care and the development of the offspring in a rodent model. Biol Psychiatry 59:1227-35.

Chung SR, McCabe JT, Pfaff DW (1991) Estrogen influences on oxytocin mRNA expression in

preoptic and anterior hypothalamic regions studied by in situ hybridization. J Comp Neurol 307:281–295.

Dellovade T, Zhu Y, Pfaff D (1999) Thyroid hormones and estrogen affect oxytocin gene expression in hypothalamic neurons. J Neuroendocrinol 11:1–10.

Dettmer AM, Novak MA, Suomi SJ, Meyer JS. (2012) Physiological and behavioral adaptation to relocation stress in differentially reared rhesus monkeys: Hair cortisol as a biomarker for anxiety-related responses. Psychoneuroendocrinology 37:191-199.

Erickson K, Gabry KE, Lindell S, Champoux M, Schulkin J, Gold P, Suomi SJ, Higley JD. (2005) Social withdrawal behaviors in nonhuman primates and changes in neuroendocrine and monoamine concentrations during a separation paradigm. Dev Psychobiol. 46:331-9.

Farah MJ (2017) The neuroscience of socioeconomic status: correlates, causes, and consequences Neuron 96:56-71.

Folstein S, Rutter M. Infantile autism: a genetic study of 21 twin pairs (1977) J Child Psychol Psychiatry 18:297-321.

Goldman S (2013) Opinion: Sex, gender and the diagnosis of autism – A biosocial view of the male preponderance. Res Autism Spectr Disord 7: 675-679.

Gould E, Daniels DC, Cameron HA, McEwen BS (1992a) Expression of adrenal steroid receptors by newly born cells and pyknotic cells in the dentate gyrus of the postnatal rat. Mol Cell Neurosci 3: 44-48.

Gould E, Cameron HA, Daniels DC, Woolley CS, McEwen BS (1992b) Adrenal hormones suppress cell division in the adult rat dentate gyrus, J Neurosci 12:3642-3650.

Guerville M, Boudry G (2016) Gastrointestinal and hepatic mechanisms limiting entry and dissemination of lipopolysaccharide into the systemic circulation. Am J Physil Gastrointest Liver Physiol 311: G1-G15.

Hallmayer J, Cleveland S, Torres A, Phillips J, Cohen B, Torigoe T, Miller J, Fedele A, Collins J, Smith K, Lotspeich L, Croen LA, Ozonoff S, Lajonchere C,Grether JK, Risch N. (2011) Genetic heritability and shared environmental factors among twin pairs with autism. Arch Gen Psychiatry 68:1095-102.

Heavey L, Phillips W, Baron-Cohen S, Rutter M. (2000) The Awkward Moments Test: a naturalistic measure of social understanding in autism (2000) J Autism Dev Disord. 30:225-36.

Hunter RG, McCarthy KJ, Milne TA, Pfaff DW, McEwen BS (2009) Regulation of hippocampal H3 histone methylation by acute and chronic stress. Proc Natl Acad Sci 109:17657–17662.

Hunter RG, Murakami G, Dewell S, Seligsohn M, Baker ME, Datson NA, McEwen BS, Pfaff DW(2012) Acute stress and hippocampal histone H3 lysine 9 trimethylation, a retrotransposon silencing response. Proc Nat Acad Sci 109(43):17657–17662.

Hunter R, Gagnidze K, McEwen B, Pfaff D (2015) Stress and the dynamic genome: steroids, epigenetics and the transposome. Proc Natl Acad Sci 112:6828–6833.

Kow L-M, Johnson AE, Ogawa S, Pfaff DW (1991) Electrophysiological actions of oxytocin on hypothalamic neurons, in vitro: neuropharmacological characterization and effects of ovarian steroids. Neuroendocrinology 54:526–535.

Kow, L-M, Pfaff DW (2016a) Rapid estrogen actions on ion channels: A survey in search for mechanisms. Steroids, 111: 46-53.

Kow L-M, Pataky S, Dupré C, Phan A, Martin-Alguacil, N, Pfaff, DW (2016b) Analyses of rapid estrogen actions on rat ventromedial hypothalamic neurons. Steroids 111: 100-112.

Magariños AM, Li CJ, Gal Toth J, Bath KG, Jing D, Lee FS, McEwen BS (2011) Effect of brain-derived neurotrophic factor haploinsufficiency on stress-induced remodeling of hippocampal neurons. Hippocampus 21: 253-264.

Magariños AM, McEwen BS, Flügge G Fuchs E (1996) Chronic psychosocial stress causes apical dendritic atrophy of hippocampal CA3 pyramidal neurons in subordinate tree shrews. J Neurosci 16: 3534-3540.

Magariños AM, Pfaff DW (2016) Sexual motivation in the female and its opposition by stress Curr Top Behav Neurosci 27:35-49.

Magariños AM, Verdugo JM, McEwen BS (1997) Chronic stress alters synaptic terminal structure in hippocampus. Proc Natl Acad Sci USA 94: 14002-14008.

Majewska M D, Harrison N L, Schwartz, R D, Barker, J L, Paul, S M (1986). Steroid hormone metabolites are barbiturate-like modulators of the GABA receptor. Science 232, 1004-1007.

McCarthy MM, Chung SR, Ogawa S, Kow L-M, Pfaff DW (1991) Behavioral effects of oxytocin: is there a unifying principle? In: Jard S, Jamison R (eds) Vasopressin. Colloque INSERM/John Libbey Eurotext Ltd. vol 208, pp. 195–212.

McEwen BS (2016) A key role for allostatic overload in ASD and other disorders. Commentary on "An integrative model of autism spectrum disorder: ASD as a neurobiological disorder of experienced environmental deprivation, early life stress, and allostatic overload" by William M. Singletary, MD, Neuropsychoanalysis 18: 9-14.

McEwen BS (2007) Physiology and neurobiology of stress and adaptation: central role of the brain. Physiol Rev 87:873-904.

McEwen BS (1998) Protective and damaging effects of stress mediators. N Engl J Med 338:171-179.

Pfaff DW, Martin E, Ribeiro AC (2007) Relations between mechanisms of CNS arousal and mechanisms of stress. Stress 10: 316-325.

Pfaff DW, Rapin I, Goldman S (2011) Male predominance in autism: neuroendocrine influences on arousal and social anxiety. Autism Research 4: 163-176.

Quiñones-Jenab V, Jenab S, Ogawa S, Adan RAM, Burbach PH, Pfaff DW (1997) Effects of estrogen on oxytocin receptor messenger ribonucleic acid expression in the uterus, pituitary and forebrain of the female rat. Neuroendocrinology 65: 9–17.

Rutter ML. (2011) Progress in understanding autism: 2007-2010. J Autism Dev Disord. 41:395-404.

Schaafsma SM, Gagnidze K, Reyes A, Norstedt N, Månsson K, Francis K, Pfaff DW (2017) Sex-specific gene-environment interactions underlying ASD-like behaviors Proc Natl Acad Sci USA 114:1383-1388.

Schaafsma SM, Pfaff DW (2014) Etiologies underlying sex differences in Autism Spectrum Disorders/ Front Neuroendocrinol 35: 255-271.

Schreuder L, Eggen BJ, Biber K, Schoemaker RG, Laman JD, de Rooij SE (2017) Pathophysiological and behavioral effects of systemic inflammation in aged and diseased rodents with relevance to delirium: A Systematic review. Brain Behav Immun 62: 362-381.

Schulze HG, Gorzalka BB (1991) Oxytocin effects on lordosis frequency and lordosis duration following infusion into the medial preoptic area and ventromedial hypothalamus of female rats. Neuropeptides 18:99–106.

Schumacher M, Coirini H, Pfaff DW, McEwen BS (1990) Behavioral effects of progesterone associated with rapid modulation of oxytocin receptors. Science 250:691–694.

Schumacher M, Coirini H, Flanagan LM, Frankfurt M, Pfaff DW, McEwen BS (1992) Ovarian steroid modulation of oxytocin receptor binding in the ventromedial hypothalamus. In: Pedersen CA et al (eds) Oxytocin in maternal, sexual, and social behaviors. Annals, New York Academy of Sciences, vol 652, pp 374–386.

Schumacher M, Zhu X and Guennoun R (2017) Progesterone synthesis, metabolism and mechanisms of action and effects in the nervous system. In (Pfaff, D., & Joels, M., editors) Hormones, Brain and Behavior (3rd edition). London: Academic Press/Elsevier, volume 3, pp;.215-245.

Selye H (1946) The general adaptation syndrome and the diseases of adaptation. J Clin Endocrin Metab, 6:117-230.

Uphouse L, Hiegel C (2013) An antiprogestin, CDB4124, blocks progesterone's attenuation of the negative effects of a mild stress on sexual behavior. Behav Brain Res 240:21–25.

Van der Poll T, Coyle SM, Barbosa K, Braxton CC, Lowry SF (1996) Epinephrine inhibits tumor necrosis factor-α and potentiates interleukin 10 production during human endotoxemia. J Clin Invest 97:713-719.

Weaver, I.C., N. Cervoni, F.A. Champagne, A.C. D'Alessio, S. Sharma, J.R. Seckl, S. Dymov, M. Szyf, and M.J. Meaney, Epigenetic programming by maternal behavior (2004) Nat Neurosci, **7**: 847-54.

Whirledge S, Cidlowski JA (2013) A role for glucocorticoids in stress-impaired reproduction: Beyond the hypothalamus and pituitary. Endocrinology 154:4450–4468.

White S, Uphouse L (2004) Estrogen and progesterone dose-dependently reduce disruptive effects of restrain on lordosis behavior. Horm Behav 45:201–208.

.

Highlights

- A leading figure in the neurobiology of stress has been Bruce S. McEwen, professor at Rockefeller University.
- One application of stress-related neuroscience shows interference with reproductive processes in female laboratory rodents.
- Another application of stress-related neuroscience is that early stress contributes to the development of autism.