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Don't worry; be informed about the epigenetics of anxiety☆

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ABSTRACT

Epigenetic processes regulate gene expression independent of the DNA sequence and are increasingly being investigated as contributors to the development of behavioral disorders. Environmental insults, such as stress, diet, or toxin exposure, can affect epigenetic mechanisms, including chromatin remodeling, DNA methylation, and non-coding RNAs that, in turn, alter the organism's phenotype. In this review, we examine the literature, derived at both the preclinical (animal) and clinical (human) levels, on epigenetic alterations associated with anxiety disorders. Using animal models of anxiety, researchers have identified epigenetic changes in several limbic and cortical brain regions known to be involved in stress and emotion responses. Environmental manipulations have been imposed prior to conception, during prenatal or early postnatal periods, and at juvenile and adult ages. Time of perturbation differentially affects the epigenome and many changes are brain region-specific. Although some sex-dependent effects are reported in animal studies, more research employing both sexes is needed particularly given that females exhibit a disproportionate number of anxiety disorders. The human literature is in its infancy but does reveal some epigenetic associations with anxiety behaviors and disorders. In particular, effects in monoaminergic systems are seen in line with evidence from etiological and treatment research. Further, there is evidence that epigenetic changes may be inherited to affect subsequent generations. We speculate on how epigenetic processes may interact with genetic contributions to inform prevention and treatment strategies for those who are at risk for or have anxiety disorders.

1. Anxiety disorders

Anxiety disorders are characterized by excessive worry and avoidance that cause significant impairment across multiple domains of an individual's life (e.g., school, home, work; American Psychiatric Association, 2013). Children and young adults (ages 10–25 years old) are at highest risk for developing anxiety disorders and almost one third of the child and adult population meets criteria for an anxiety disorder (28.8%; Michael et al., 2007). Although animal models are unable to capture cognitive processes related to anxiety (i.e., worry), studies have examined various behaviors as proxies for anxiety (e.g., decreased interest in social engagement, increased hiding in dark spaces, decreased time to feed). These animal studies, and recent human studies, are beginning to provide insight to the epigenetic mechanisms underlying the emergence and maintenance of anxiety.

The current diagnostic classification system, the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5; American Psychiatric Association, 2013), outlines criteria for eleven anxiety disorders including panic disorder and social anxiety disorder, that are described later in this review. In DSM-5, panic disorder is described as an abrupt surge in physiological (e.g., sweating, shaking, chest pain) or cognitive (e.g., fear of losing control or going "crazy") symptoms. Social anxiety is described as marked fear or anxiety about one or more social situations in which the individual is exposed to possible scrutiny by others. Notably, the human studies described herein only examine panic and social anxiety disorders – other human studies examine "anxiety symptoms" or sub-diagnostic anxiety symptoms. Further, no studies included in the current review examine the high comorbidity of anxiety with other disorders, particularly with depression, that is estimated to be present in more than half (57%) of individuals with an anxiety disorder (Zimmerman et al., 2014). Current treatments (e.g., cognitive-behavioral therapy) for anxiety appear effective in the short-term; however, they have yet to prove efficacious in maintaining these short-term therapeutic gains (Piacentini et al., 2014). The efficacy of pharmacotherapy (e.g., barbiturates and benzodiazepines) is complicated by these high comorbidity rates. As such, better biological insight is needed into the epigenetic processes that underlie the development of

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anxiety disorders. To this end, several investigations have shed light on epigenetic mechanisms that govern the regulation of genes that contribute to anxiety states. These investigations vary widely in research design, including differences across experimental manipulations, age, brain regions, and genes of interest (Table 1). As a result, we attempted to synthesize the literature according to overlapping features whenever possible. Thus, the review of the animal (preclinical) literature on epigenetics and anxiety is organized by developmental period and brain region. Then, human studies are discussed.

2. Neural correlates of anxiety

Animal models have assessed anxiety (Table 2) and associated epigenetic modifications in several brain regions. Not surprisingly, significant attention focuses on structures that regulate the stress response such as the hippocampus, amygdala, hypothalamus, and the pituitary. Striatal regions, such as the caudate-putamen and nucleus accumbens (NAc) known for regulating reward-related behaviors, emotional states and stress responses, have been investigated as well. Additionally, epigenetic alterations within cortical areas that mediate higher cognitive functions and are important in anxiety are beginning to be examined.

The neuroendocrine system is an important regulator of the stress response. Corticotropin-releasing hormone (CRH, also known as corticotropin-releasing factor or CRF) is released from the paraventricular nucleus (PVN) of the hypothalamus into the primary capillary plexus of the hypothalamo-hypophyseal portal system to stimulate the anterior pituitary to synthesize proopiomelanocortin (POMC) and release adrenocorticotropic hormone (ACTH), a peptide derived from POMC, into the blood. ACTH in the blood then activates the synthesis and release of corticosterone in rodents and cortisol in humans from the adrenal glands of the kidneys. Cortisol, or corticosterone, then feeds back on the hypothalamus and pituitary as well as the hippocampus to shut down the hypothalamic–pituitary–adrenal (HPA) axis. Dysregulation of this neurochemical system contributes to anxiety.

The contribution of genetic variance to develop an anxiety disorder is estimated to range from 30 to 50% (Hettema et al., 2001; Smoller et al., 2009) implying that 50–70% of the variance may be due to the environment. The role of environmental factors in the development of anxiety disorders may act through epigenetic mechanisms. Such

Table 2
Preclinical models of anxiety.

Test	Indices of anxiety-like behavior	Reference
Elevated Plus Maze (EPM)	↑ time/entries into closed arms ↓ time/entries into open arms	Montgomery (1955)
Open Field	↓ time/entries into center zone ↑ time/entries in peripheral zones	Hall and Ballachey (1932)
Light-Dark Box	↑ time/entries into dark chamber ↓ time/entries into light chamber	Crawley and Goodwin (1980)
Novelty-induced Hypophagia	↑ latency to feed	Dulawa and Hen (2005)
Novel Environment (stickleback fish)	↑ thigmotaxis	Maximino et al. (2010)

Table 1
Genes studied in the epigenetics of anxiety.

Gene	Product	Species	Function
Avp	Arginine vasopressin	Rodent	Posterior pituitary hormone with role in cognition, maternal behavior, etc.
Bcl11a	B-Cell CLL/Lymphoma 11 A	Rodent	Zinc finger protein involved in neuroplasticity
Bdnf	Brain-derived neurotrophic factor	Rodent	Growth factor involved in neuroplasticity
Crh	Corticotrophin releasing hormone	Rodent	Stress response hormone
Crhr1	Corticotropin releasing hormone receptor 1	Rodent	G-protein coupled receptor (GPCR) for corticotrophin releasing hormone
Crybb1	Crystallin, beta B1	Rodent	Mediates cellular homeostasis in response to stressors
Egr1	Early growth response 1	Rodent	Transcriptional regulator with role in neuroplasticity
Fgf2	Fibroblast growth factor 2	Rodent	Growth factor involved in neuroplasticity
Fkbp5	FK506 binding protein 5	Rodent	Interacts with corticoid receptor complexes
Gad1	Glutamate decarboxylase 1	Rodent	Synthesis of γ-aminobutyric acid from L-glutamic acid
GAD1		Human	
Gadd45b	Growth arrest and DNA-damage-inducible, beta	Rodent	Stress response by activation of the p38/JNK pathway
Htr1a	5-HT1_A receptor	Rodent	Inhibitory GPCR mediating serotonin neurotransmission
Jag1	Jagged1	Rodent	Cell surface receptor involved in Notch signaling
Kap1 (*Trim28*)	KRAB-associated protein 1	Rodent	Transcriptional corepressor (tripartite motif containing 28)
MAOA	Monoamine oxidase A	Human	Catalyzes oxidative deamination of amines (e.g., serotonin, dopamine, and norepinephrine)
Kmt2a	Lysine (K)-specific methyltransferase 2A	Rodent	Regulates H3K4me3 activity
Nr3c1	Nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)	Rodent	Glucocorticoid receptor and transcriptional activator
Nr4a1	Nuclear receptor subfamily 4, group A, member 1 (nerve growth factor IB)	Rodent	Transcription factor involved in neuroplasticity
Ntsr1	Neurotensin receptor 1	Rodent	GPCR with role in hypertension, thermal regulation, antinociception, etc.
Oprm1	μ-Opioid receptor	Rodent	GPCR receptor for opioids and is involved in analgesia, reward, emotions, stress, etc.
OXTR	Oxytocin receptor	Human	GPCR with role in attachment and lactation
Peg3	Paternally-expressed 3	Rodent	Imprinted transcription factor gene involved in fetal growth and nurturing behaviors
Pomc	Proopiomelanocortin	Rodent	Precursor of peptides involved in steroidogenesis, stress, energy homeostasis, immune modulation, etc.
Rln	Reelin	Rodent	Glycoprotein with role in synaptic plasticity and neuronal migration
SLC6A4	Solute carrier family 6, member 4	Human	Transports serotonin from synaptic cleft into
Slc6a4	(serotonin transporter, 5-HTT)	Rodent	presynaptic neuron
SLC6A2	Solute carrier family 6, member 2 (norepinephrine transporter, NET)	Human	Transports norepinephrine from synaptic cleft into presynaptic neuron
Syn1	Synapsin I	Rodent	Neuronal phosphoprotein on cytoplasmic surface of synaptic vesicles that may modulate neurotransmitter release
Mkrn3	Makorin ring finger protein 3	Rodent	Paternally imprinted gene encoding a putative ribonucleoprotein
Pcdhb6	Protocadherin beta 6	Rodent	Integral plasma membrane proteins with role in determining neural connections