Chapter 2
How Does Stress Work? The Role of Memes in Epigenesis

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Since Selye's work on the role of stress on the activation of the adrenal cortex and the *general adaptation syndrome* (Selye, 1956), there has been an explosion of knowledge concerning the effects of stress on the organism in such fields as neuropsychoendocrinology and neuropsychoimmunology.

2.1 Stress, Aging, and Disease

Classically, stress response is the "fight–flight" reaction to a threatening stimulus such as a dangerous animal, mugger, or approaching fire. It is accompanied with the activation of the autonomic nervous system and hypothalamo-pituitary-adrenal (HPA) axis. The organism needs the normal stress response to survive such danger situations, and inadequate or excessive adrenocortical and autonomic response is deleterious for health and survival. The active process by which the body responds to stresses and maintains homeostasis has been termed allostasis (achieving stability through change) (Sterling and Eyer, 1988). The term *allostatic load or overload* has been introduced by McEwen to denote the wear and tear and resulting pathophysiology from insufficient management of allostasis either due to too much stress or inappropriate stress response (McEwen, 1998).

When the stress is of short duration, and the behavioral, endocrine, and autonomic responses have been successful in warding off the danger situation, the organism may be strengthened by the stress experience. On the other hand, if the

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stress is prolonged and/or the organism is unable to master it (allostatic overload), there may be serious health consequences.

Sapolsky et al. proposed the *glucocorticoid cascade hypothesis* of stress and aging (Sapolsky et al., 1986). Aging animals have impaired ability to terminate the secretion of adrenocortical stress hormones at the end of stress, which may be due to the degeneration of negative feedback neurons. These neurons may further degenerate due to the toxic effects of excessive glucocorticoids, resulting in a feed-forward cascade with potentially serious pathophysiological consequences in the aged subject.

Epel and her colleagues found that perceived stress and chronicity of stress in healthy premenopausal women were significantly associated with higher oxidative stress, lower telomerase activity and shorter telomere length, which are known determinants of cell senescence and longevity in peripheral blood mononuclear cells. They found that women with the highest levels of perceived stress had shorter telomeres on average by the equivalent of at least one decade of additional aging (Epel et al., 2004).

The role of stress in various disease conditions from cancer to cardiac disease has been elucidated in numerous publications – as of this writing, there were more than 18,000 PubMed publications for stress and cancer, and more than 32,000 publications on stress and heart disease. As for the stress and the brain, there were more than 30,000 PubMed publications.

Posttraumatic stress disorder and *acute stress disorder* are results of massive identifiable stress and are manifested by emotional and behavioral symptoms. As we have seen, however, stress plays a prominent role in depression and anxiety, and, in fact, most psychiatric conditions are either precipitated by or contributed by stress. Even exacerbations of schizophrenia, often thought to be primarily biological, are induced by emotional stress (Marom et al., 2005).

2.2 Stress, Memes, and the Brain

Stress has been shown to change both the structure and function of the brain.

When a stimulus arrives at a sensory cortical area such as the visual cortex, auditory cortex (Wernicke's area), and/or the somatosensory postcentral gyrus and the thalamus, the neural impulses are projected to the association cortices resulting in a perception. Perception is determined by both genetically determined circuitry and neural projections determined by learning and memory formation, i.e., memes (see Section 2.5 and Chapter 8).

Then the cortical impulses constituting the percepts are projected to the amygdala, the hippocampus, and other limbic structures, all of which are interconnected with each other. Amygdala has a very tight feedback loop with the anterior cingulate gyrus which is connected with the thalamus, neocortex, and the entorhinal cortex. The negative feedback from the anterior cingulate reduces amygdalar activation. Stressful perceptions stimulate amygdala and result in the autonomic and

HPA activation. In memetic terms, the perceived human face (meme) arising in the primary visual cortex and arriving at amygdala may be elaborated into a *smiling* human face, the attribute meme of "smiling" coming from the anterior cingulate gyrus after processing of the original stimulus.

Hippocampus plays an important role in shutting off the HPA activation – any damage or atrophy of the hippocampus attenuates this resulting in a prolonged HPA activation to stress (McEwen, 2007). Longitudinal studies on aging in human subjects revealed that progressive increases in salivary cortisol during a yearly exam over a 5-year period predicted reduced hippocampal volume and reduced performance on hippocampal-dependent memory tasks (Lupien et al., 1998). Initially, it was thought that aging in hippocampus was associated with a loss of neurons, but subsequent studies on animal models of aging confer greater importance to a loss of synaptic connectivity or impairment of synaptic function (McEwen, 2007).

Neural regeneration is now known to occur in the brain, particularly in hippocampus. Certain types of acute stress and many chronic stressors suppress neurogenesis or cell survival in the dentate gyrus of the hippocampus. Glucocorticoids, excitatory amino acids acting on NMDA receptors, and endogenous opioids mediate the suppression (Gould et al., 1997). Stress also affects the shape and abundance of dendrites in the hippocampus, amygdala, and prefrontal cortex. Generally, stress results in retraction and simplification of dendrites. In memetic terms, stress memes tend to disconnect incoming memes from existing memes (memories).

Puberty seems to be a particularly vulnerable period for the effect of stress on the brain. Stress in peripubertal rats resulted in a stunting of growth in parts of the hippocampus and a sustained down-regulation of the hippocampal glucocorticoid receptor (GR) gene expression, resulting in deficits in the shut-off of the HPA activation. Daily infusions of corticosterone during puberty resulted in a reduction of both hippocampal volume and the number of neurons in parts of the hippocampus, while it produced only reduction in volume but not in the number of neurons in adults (McEwen, 2007).

Corticosteroids released by HPA activation interact with many chemicals and neurotransmitters in the hippocampus, including serotonin, endorphins, GABA-benzodiazepine receptors, and glutamate and other excitatory amino acids. Chronic stress in rats releases glutamate and affects the neural cell adhesion molecule (NCAM, PSA-NCAM). Chronic stress also releases the tissue plasminogen activator (tPA), an extracellular protease and signaling molecule, that is involved in the loss of spines and NMDA receptor subunits in the hippocampus (McEwen, 2007).

Neurotrophic factors such as brain-derived neurotrophic factor (BDNF) play a role in dendritic proliferation. BDNF knockout mice exhibit a paucity in dendrites and no further reduction in hippocampal dendritic length with chronic stress, while wild-type mice show reduced dendritic length with chronic stress. On the other hand, overexpression of BDNF prevents stress-induced dendritic reductions and an antidepressant-like action on forced swimming test in mice (Govindarajan et al.,

2006). Both stress-induced increases and decreases of BDNF expression have been reported, which may reflect that BDNF synthesis may be triggered by stress to offset the depletion of BDNF caused by stress. BDNF and corticosteroids may oppose each other, with BDNF reversing the corticosteroid-induced reduction in hippocampal neuronal sensitivity. BDNF may facilitate meme introduction, replication, and synthesis.

Corticotropin-releasing factor (CRF) plays an important role in mediating stress in the brain. It regulates the ACTH release in the pituitary and also acts on the amygdala that controls the behavioral and autonomic responses to stress including the release of tPA that plays an important part in anxiety. When CRF is injected into the brain, it produces arousal and increased responsiveness to stressful stimuli that seem to be independent of the pituitary adrenal axis and can be reversed by specific and selective CRF antagonists. Such antagonists also reverse behavioral responses to stressors. An interaction between the norepinephrine and the CRF systems seems to occur both at the locus ceruleus and the amygdala. Noradrenergic neurons arising from the locus ceruleus are concerned with behavioral arousal and anxiety. CRF neurons seem to activate locus ceruleus. Norepinephrine, in turn, may stimulate CRF release in the paraventricular nucleus of the hypothalamus, the bed nucleus of the stria terminalis, and the central nucleus of the amygdala. Such a feed-forward system was hypothesized to be particularly important in stress situations where an organism must mobilize not only the HPA but also the central nervous system. Such a positive feedback system that accelerates anxiety response, however, might be particularly vulnerable to dysfunction (Koob, 1999).

Prefrontal cortex and amygdala are also affected by stress. Chronic stress in rats causes dendritic shortening in the medial prefrontal cortex but dendritic growth in the neurons in amygdala and in the orbitofrontal cortex. Glucocorticoids have been shown to produce retraction of dendrites in medial prefrontal cortex. Behaviorally, chronic stress remodeling of the prefrontal cortex impairs attention set shifting (McEwen, 2007). Chronic stress enhances amygdala-dependent unlearned fear and fear conditioning (Conrad et al., 1999). Chronic stress also increases aggression through hyperactivity of amygdala.

The amygdala exerts a regulatory influence on the stress response and is itself affected by stress. The serine protease tissue plasminogen activator (tPA), a key mediator of dendritic spine plasticity, is required for stress-induced facilitation of anxiety-like behavior. In the tPA knockout mice, repeated stress did not cause a reduction in the spine density (Bennur et al., 2007). BDNF may also play a role in amygdala in enhancing anxiety and increasing dendritic density.

All the brain structures mentioned, the prefrontal cortex, amygdala, and hippocampus, are closely interconnected and influence each other. Inactivation of amygdala blocks stress-induced impairment of hippocampal memory long-term potentiation (LTP) and spatial memory (Kim et al., 2005). Stimulation of medial prefrontal cortex reduces responsiveness of central amygdala output neurons and thus the prefrontal cortex plays an important role in fear extinction. Amygdala–hippocampus connections are required for the processing of emotional memories with contextual information (McEwen, 2007).

2.3 Role of Stress and Nurturing in Development: Epigenesis

Development is considered to be *epigenetic*, i.e., it occurs as an interaction between genes and environment. The phenotypic expression of a gene, i.e., whether it will be turned on or off in the life of an organism, depends on the organism's interaction with the environment. Stress figures in prominently in this epigenetic model of development. As I discussed in the previous chapter, the effect of childhood stress on the serotonin transporter promoter gene (5-HTTLPR) has been demonstrated and that noxious effects may be mitigated by good mothering in childhood at least in monkeys. But how exactly does stress affect the genes?

In a series of experiments, Szyf et al. (2007), Unterberger et al. (2006), Weaver (2007), and Weaver et al. (2007) studied the effects of different maternal behavior in rats. Maternal behavior in rats affects the neural systems that tonically inhibit corticotrophin-releasing factor (CRF) synthesis and release in the hypothalamus and amygdala, which in turn activate central norepinephrine in response to stress. Glucocorticoids initiate tonic negative feedback inhibition over CRF synthesis and release and thus dampen HPA responses to stress. This glucocorticoid negative feedback is, in part, mediated by glucocorticoid receptors (GR) which are found in many brain areas including hippocampus.

As adults, the offspring of high licking and grooming (LG) mothers show increased hippocampal GR expression and enhanced glucocorticoid feedback sensitivity by comparison to adult animals reared by low-LG mothers. Thus, adult offspring of high-LG mothers show decreased hypothalamic CRF expression and more modest HPA responses to stress. Eliminating the difference in hippocampal GR levels abolishes the effects of early-life experience on HPA.

In essence, the experience of high licking by the rat pup is a meme that forms neural connections as perception that in turn activates existing memes and the ensemble of memes increases hippocampal GR expression.

In addition to alterations in hippocampal GR expression, enhanced maternal LG behavior over the first week of life is associated with increased hippocampal neuronal survival, synaptogenesis, and improved cognitive performance under stressful conditions. Behaviorally, such pups become "neophilic" rats that are more exploratory in novel environments and less emotionally reactive. On the other hand, the pups with lower LG during their first week of life develop a "neophobic" phenotype with increased emotional and HPA reactivity and less exploration of a novel situation (McEwen, 2007).

When the pups of high-LG mothers were bred by low-LG mothers, and pups of low-LG mothers were bred by high-LG mothers (cross-breeding), the gene expression and stress response patterns followed what was expected of the early experience, i.e., the fostering mother's care, not the biological mother, determined the degree of gene expression and stress response.

How could the behavior of the caregiver cause a stable change in gene expression in the offspring long after the caregiver is gone? Szyf et al. propose an epigenetic mechanism in which the maternal behavior of the caregiver triggered an epigenetic change in the brain of the offspring.

2.4 Environment Changes Epigenome

The epigenome consists of the chromatin and its modifications and a covalent DNA modification through methylation. The DNA is wrapped around a protein-based structure termed chromatin. The basic building block of chromatin is the nucleosome, which is formed of an octamer of histone proteins. There are five basic forms of histone proteins. The histones are extensively modified by methylation, phosphorylation, acetylation, and ubiquitination, and such modifications play an important role in defining the accessibility of the DNA wrapped around the nucleosome core. The specific pattern of histone modifications forms a "histone code," that determines the parts of the genome to be expressed at a given point in time in a given cell type (Jenuwein and Allis, 2001; Taverna et al., 2007). Thus a change in histone configurations around a gene will change its level of expression and could switch a gene between functionality and "silence."

In addition to chromatin, the DNA molecule itself is modified by methylation of the cytosine rings in the dinucleotide sequence CG in vertebrates (Razin, 1998; Razin and Kantor, 2005) (Fig. 2.1). In the vertebrate genome, DNA methylation occurs in different patterns in different cell types. Since DNA methylation is part of the chemical structure of the DNA itself, it is more stable than other epigenetic markers. It is generally accepted that DNA methylation plays an important role in regulating gene expression. The methylation of DNA in distinct regulatory regions is believed to mark silent genes. Epigenomic screening of human chromosomes suggests that a third of the genes analyzed shows inverse correlation between the state of DNA methylation at the 5′ regulatory regions and the gene expression (Eckhardt et al., 2004, 2006; Lesche and Eckhardt, 2007). Aberrant silencing of tumor suppressor genes by DNA methylation seems to be a common mechanism in cancer (Baylin, 2001; Rountree et al., 2001).

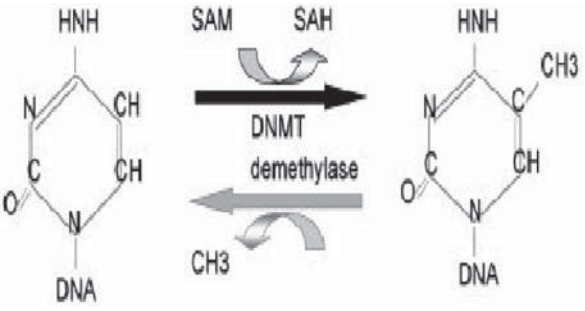

Fig. 2.1 The reversible DNA methylation reaction. DNA methyltransferases (DNMT) catalyze the transfer of methyl groups from the methyl donor *S*-adenosylmethionine to DNA releasing *S*-adenosylhomocysteine. Demethylases release the methyl group from methylated DNA as either methanol or formaldehyde. (From Szyf et al., 2007, reprinted with permission)

The DNA methylation pattern is established during early development and is maintained faithfully through life. It was long believed that DNA methylation pattern could be altered only during cell division when new unmethylated DNA is synthesized and serves as a substrate for maintenance DNA methyltransferase (DNMT). There is evidence, however, that DNMT exists in post-mitotic cells and that DNMT levels in neurons change in certain pathological conditions such as psychosis (Veldic et al., 2005). DNA methylation pattern probably represents a balance of methylation and demethylation in response to physiological and environmental signals.

The epigenome consisting of both histone configurations and DNA methylation status determines the accessibility of the transcription machinery (Szyf et al., 2007) and thus determines which genes are accessible for transcription (see Figs. 2.1, 2.2,

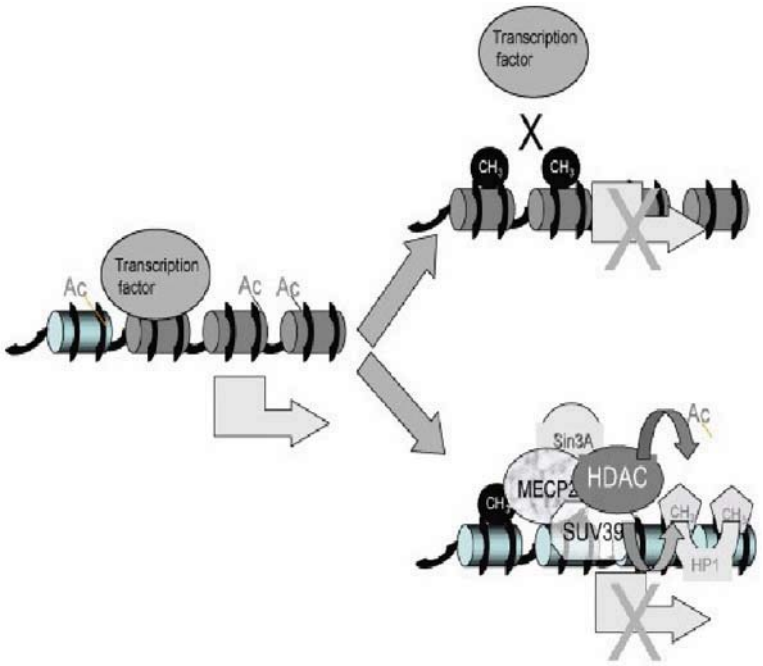

Fig. 2.2 Two mechanisms of silencing gene expression by DNA methylation. An expressed gene (transcription indicated by *horizontal arrow*) is usually associated with acetylated histones and is unmethylated. An event of methylation would lead to methylation by two different mechanisms. The methyl group (CH_3) interferes with the binding of a transcription factor which is required for gene expression resulting in blocking of transcription. The second mechanism shown in the *bottom right* is indirect. Methylated DNA attracts methylated DNA binding proteins such as Me CP2, which in turn recruits co-repressors such as SIN3A, histone methyltransferases such as SUV39 that methylates histones and histone deacetylases (HDAC), which remove the acetyl group from histone tails. Methylated histones (K9 residue of histone tails) recruit heterochromatin proteins such as HP1, which contribute to a closed chromatin configuration and silencing of the gene. (From Szyf et al., 2007, reprinted with permission)

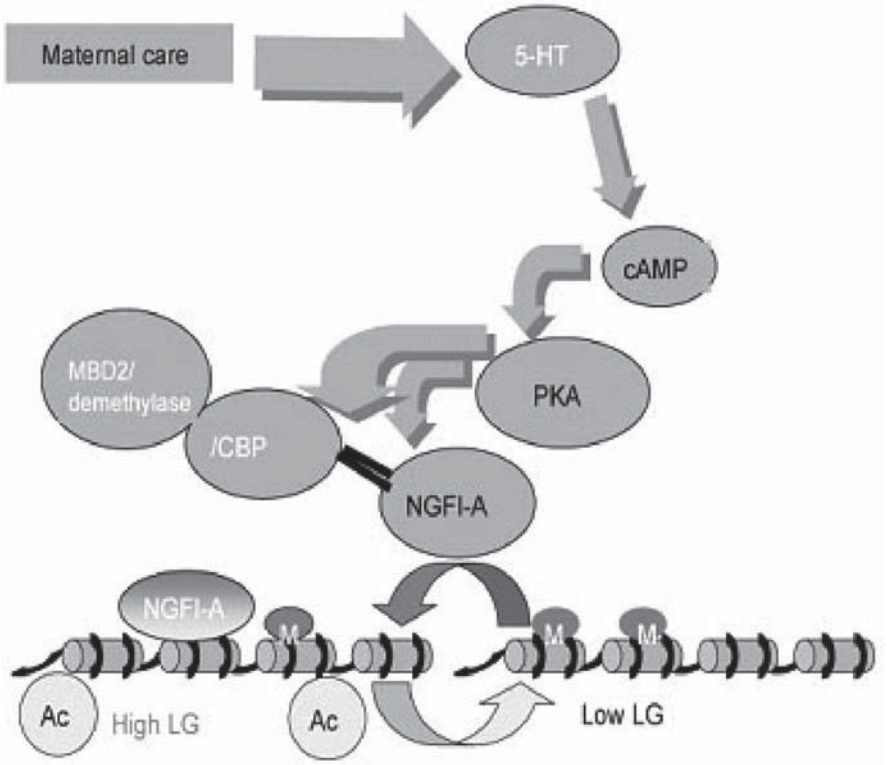

Fig. 2.3 Behavioral gene programming by maternal care. The sequence of events leading from maternal licking and grooming behavior to epigenetic programming of the GR exon 1, promoter CBP, a HAT (cAMP recognition element-binding protein, CREB), M, methylated CG, Ac, acetylated H3-Histone. (From Szyf et al., 2007, reprinted with permission)

and 2.3). Inaccessible genes are, therefore, silent whereas accessible genes are transcribed. In addition, another level of epigenetic regulation by small, non-coding RNAs (microRNAs) has recently been described (Bergmann and Lane, 2003).

Returning to the mechanisms of early experience affecting stress responsivity, maternal programming of individual differences in gene expression and stress responses in the rat seems to involve modifications of epigenetic mechanisms, including DNA methylation and histone modification of a nerve growth factor inducible protein A (NGFI-A) transcription factor binding site on a brain-specific GR promoter. Increased maternal LG behavior during the first week of life causes DNA demethylation, increased histone acetylation and NGFI-A binding, and increased hippocampal GR expression (Weaver et al., 2006). Thus, the NGFI-A binding site on the hippocampal GR promoter is methylated and hypoacetylated in offspring of low-LG mothers and demethylated and hyperacetylated in offspring of high-LG mothers.

Weaver et al. also report that the central infusion of the histone deacetylase inhibitor trichostatin A (TSA) eliminated the maternal effect on histone acetylation, DNA methylation, hippocampal GR expression, and HPA responses to stress in the adult offspring of low-LG mothers (Weaver et al., 2004). On the other hand, central infusion of the adult offspring of high-LG mothers with a methyl donor, L-methionine, a precursor to *S*-adenosylmethionine, resulted in increased methylation of the NGFI-A binding site on the hippocampal GR promoter, decreased GR expression, and increased HPA responses to stress (Weaver et al., 2005).

The difference in the methylation status between the offspring of high- and low-LG mothers emerged over the first week of life, was reversed with cross-fostering, and persisted into adulthood. Weaver et al. have also shown that maternal care early in life affected the expression of hundreds of genes in the adult hippocampus (Weaver et al., 2006).

Physical environment, including environmental chemicals and toxins which interact with the epigenetic machinery during this critical period might also have a profound impact on behavior later in life by interfering with the maternal care-driven epigenetic programming.

The epigenetic gene expression determined by the quality of maternal care during the first week of life seems to be potentially reversible as there is a dynamic equilibrium in methylation–demethylation reactions (Szyf et al., 2007).

The epigenetic reversal caused by TSA infusion discussed above was reported to be accompanied with a behavioral change so that the stress response of the TSA-treated adult offspring of low LG was indistinguishable from the offspring of high LG.

Such reversal of methylation could be achieved also by neurotransmitter activation that eventually stimulates histone acetyltransferases. Szyf et al. hypothesize that maternal care (LG) in early life elicits a thyroid hormone-dependent increase in serotonin (5-HT) activity at 5-HT_7 receptors, and the subsequent activation of cyclic adenosine 3′, 5′ monophosphate (cAMP) and cAMP-dependent protein kinase A (PKA), which is accompanied by increased hippocampal expression of NGFI-A transcription factor which, in turn, binds to the GR exon 1_7 promoter region. NGFI-A interacts with the transcriptional coactivator and histone acetyl transferase CREB binding protein (CBP). Signaling pathways that result in increased cAMP also activate CBP. Recruitment of CBP to the GR exon 1_7 promoter in response to maternal care could explain the increased acetylation and demethylation observed in offspring of high-LG (Szyf et al., 2007).

How does licking by mother or foster-mother affect the pup's neurotransmitter levels and gene methylation status in many parts of the brain? The perception of licking by the pup results in memes, i.e., new neural connections and potentiation of existing ones that may represent, in *homo sapiens* terms, "I am loved." It is these patterns of neural connections (memes) that affect other neural connections to result in neurotransmitter release and affect genes. The affected genes, in turn, affect the individual's perceptual bias and interpretation of life experiences in the future, and thus stress vulnerability or resilience.

Behavioral interventions which lead to firing of neurons and consistent and repetitive activation of signaling pathways might also lead to a change in DNA methylation of specific genes in the adult brain. In addition, drugs, both recreational and therapeutic, may alter DNA methylation patterns of genes in the brain. Vaproic acid, a mood stabilizer and anticonvulsant, is a histone deacetylase (HDAC) inhibitor and triggered replication-independent DNA demethylation in tissue culture, and inhibited DNA methylation in animal brain (Detich et al., 2003; Milutinovic et al., 2007; Tremolizzo et al., 2002).

2.5 Memes and Epigenesis

How does stress actually work? What is the *allo* in *allostasis?* We often talk about stress as though it is an obviously definable condition. In cases of physical stress, such as extreme heat or cold, or physical trauma, the physiologic demand may be direct and obvious, although these are also accompanied by meanings that may not be so obvious. In cases of psychological stress, however, the exact mechanism by which stress enters the body has not been well explained.

Perception obviously underlies all stress but why are certain percepts stressful to some but not others? Why do some neutral percepts, such as advertising jingles, sometimes recur in one's mind and cause annoyance?

Perceiving involves an integration of sensory impulses with an existing information base (memories) in the brain (see Chapter 9 for further discussion on this topic). Such an integration creates a percept, a bit of information that interacts with other information in the brain. Often such percepts are replicas of information from other brains or sources of information such as books, DVDs, etc.

Richard Dawkins coined the term, *memes*, to denote such bits of information that replicate themselves (Dawkins, 1976). Memes are created, stored, and replicated not only in human brains but also in computers, and replicated by copiers, fax machines, printers, and stored in books, DVDs, and other media (see Chapter 8, Chapter 9, and Chapter 10 for how memes rose, how they evolved, and exactly where they reside).

Perceiving may then be considered to be an act of meme infusion into the brain or meme creation making use of sensory input. Memes enter the brain through the *vehicle* of sensations. The perception of a stressful situation is the introduction of stress-response inducing memes. For this to occur, there has to be an interaction between the newly introduced meme and the preexisting memes, and the interaction must lead to an activation of the limbic system (resulting in emotional memes).

Is maternal behavior a meme when all she is doing is what comes instinctually? It is a meme generated by the mother either pre-programmed by genes or learned by observation of others or both. It is, however, the meme of being cared for, or licked, experienced by the pup that has long-term consequences – it is introduced into the pup through maternal behavior, and now resides in the pup as a meme, having caused gene modification and modification in the brain to interpret new experiences against the new template.

2.6 Stress Awakens Dormant Memes Resulting in Mental Illness

How does the concept of the meme clarify stress? The environment consists of memes and potential memes like a culture medium in a petri dish. The culture medium consists of molecules, some of them nutrients, some of them toxins, and others inert. Some enter the organism and become part of it or give it energy. Others may simply enter and stay without much effect. Under certain conditions, such as an increase in the concentration of the toxic molecules, some such molecules will penetrate the protective barrier of the organism and cause a reaction in the host – perhaps an immune reaction that gets rid of the toxic molecule, or the organism may succumb to the toxin. The shape and nature of the toxic molecule play important roles in whether it enters the host, and what happens afterwards. So with memes. The shapes and other characteristics of the vehicles of memes are physical in nature such as printed words, spoken words, melodies, rhythm, scenes, movements, facial expressions, touch, etc.

Memes contain various specific sensory components that can be identified and analyzed. For example, the news of the death of a loved one may be introduced into the brain in different memetic vehicles, e.g., as a phone call, a letter, a news item on TV, etc, which cause different patterns and sequence of brain activation and thus affective arousal. Thus, the sound of a phone call may reverberate (replicate) repeatedly in the brain while a visit by a friend bearing the news may be soon forgotten. Stress thus may be definable through an analysis of the types and quantities of memes and their vehicles that invade the brain.

While memes enter the brain through physical sensations, memes are bits of information, and like all information, a meme can be transcribed and translated into different languages and physical sensations. In the brain, memes are functional neuronal clusters (*neural cliques*) with specific long-term potentiation. Meme replication occurs in the brain when a meme-containing neuronal cluster is reinforced by stimulation, which may in turn infect other clusters to change configuration (see Chapter 9).

I noted in the previous section that stress changes the structure and function of the brain in various ways. The stress response in the brain may be seen to be a result of replications of stress memes triggered by the introduction of new stress memes. Memes are above all replicators. The invader in the culture medium analogy is a replicating virus. The stress memes interact with resident stress memes in the brain, which will tend to cause a cascade of stress meme replication. Counterbalancing this tendency is the host immune response, the negative feedback loop to amygdala from the cortex that may be effective in shutting off the stress response – if the protective memes are prepared and abundant. Chronic stress diminishes the number of hippocampal neurons and causes an attenuation of the hippocampal dendritic connections resulting in a disconnection between long-term memory (resident memetic store that may attenuate the stress response) and current stress meme infusion, a favorable circumstance for invasion of new memes.

The arousal and activation associated with acute stress may create a condition for heightened receptivity for meme infusion from the outside, while the deleterious

effects of chronic stress on the brain serve to protect the stress memes from resident protective memes. Dormant stress memes, however, may be activated by the incoming stress memes, especially as the protective memes are attenuated.

Recognizing memes as independent replicators whose only concern is replication of themselves regardless of consequences to the host organism can explain why allostatic overload occurs so easily in human beings, whose brains are particularly favored by memes (see Chapter 9 for a discussion of the mechanisms of meme replication in the brain).

To summarize so far, we may conceptualize mental illness as a final common pathway dysregulation syndrome of normal brain function. In the course of development, particularly in critical periods in early life, genes are turned on or off depending on stress or nurturance, giving rise to vulnerability to stress in later life. Stress is introduced into the brain as memes that interact with resident memes resulting in acute arousal that serves the adaptive fight/flight reaction and receptivity to introduction of memes. Chronic stress attenuates memory function causing a disconnection between new memes and resident protective memes that are normally dominant. The new memes may then interact with dormant or suppressed resident memes to stimulate their replication. Thus, pathogenic, hitherto suppressed memes may become dominant. In such an allostatic overload situations, dysregulation of brain function may result in a psychiatric syndrome, in which there may be an unchecked replication of pathologic memes. But how do we acquire the resident memes in the first place? From the culture medium, which will be the topic of discussion in the next chapter.

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