THEORY

Stress-Induced Alternative Gene Splicing in Mind-Body Medicine

Ernest Lawrence Rossi, PhD

Abstract

Recent research documents how psychosocial stress can alter the expression of the acetylcholinesterase gene to generate at least 3 alternative proteins that are implicated in a wide variety of normal mind-body functions, as well as pathologies. These range from early embryological development, plasticity of the brain in adulthood, post-traumatic stress disorder (PTSD), and stress-associated dysfunctions of the central nervous, endocrine, and immune systems, to age-related neuropathologies. Such stress-induced alternative gene splicing is proposed here as a major mind-body pathway of psychosocial genomics—the modulation of gene expression by creative psychological, social, and cultural processes. We explore the types of research that are now needed to investigate how stress-induced alternative splicing of the acetylcholinesterase gene may play a pivotal role in the deep psychobiology of psychotherapy, meditation, spiritual rituals, and the experiencing of positive humanistic values that have been associated with mind-body medicine, such as compassion, beneficence, serenity, forgiveness, and gratitude.

INTRODUCTION: SELYE'S VISIONARY CONCEPT OF STRESS

Hans Selye presented a visionary concept of stress in the 1956 edition of his famous book, *The Stress of Life*.[1(p304-305)]

> *Perhaps the most fascinating aspect of medical research on stress is its fundamentally permanent value to man.... The study of stress differs from research with artificial drugs because it deals with the defensive mechanisms of our own body. The immediate results of this budding new science are not yet as dramatic in their practical applications as are those of many drugs, but what we learn about nature's own self-protecting mechanisms can never lose its importance. Such defensive measures as the production of adaptive hormones by glands are built into the very texture of the body; we inherited them from our parents, and transmit them to our children, who, in turn, must hand them on to their offspring, as long as the human race shall exist. The significance of this kind of research is not limited to fighting this or that disease. It has bearing upon all diseases and, indeed, upon all human activities because it furnishes knowledge about the essence of THE STRESS OF LIFE.*

Selye's initial biological conception of stress focused on the activity of "adaptive hormones by glands [that] are built into the very texture of the body." This relationship between stress and hormones was the forerunner of our current recognition of the hypothalamic-pituitary-adrenal (HPA) axis in the psychobiological integration of mind-body medicine. Current research emerging from the human genome project traces this hormonal integration of mind and body via the HPA axis to the genomic level.[2,3] Sensory-perceptual cues of psychosocial and physical stress and trauma are communicated to the organs, tissues, and cells of the brain and body via the neural, endocrine, and immune systems. The ultimate level of adaptation to stress takes place when challenging signals from the environment are communicated to the cellular level to turn cascades of gene expression on and off. When genes are turned on by stress, the information in their DNA code is "transcribed" into messenger RNA (mRNA), which then serves as a template that is "translated" into proteins making up the structure and adaptive functions of the brain and body. Proteins, for example, regulate the structural and energy dynamics of the cell, as well as the neurotransmitters, hormones, and signals of the psychoimmune system in mind-body medicine.

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The original "Dogma of Molecular Biology" presented by Watson and Crick[4,5] 50 years ago proposed that one or more signals from the environment and/or body turned on one gene that made one protein, that modulated one molecular structure, and one adaptive physiological function. Since there are only about 35,000 genes in the human genome, however, this led to the question of how so few genes could account for the immense complexity of human adaptive behavior in health and illness. This question is now resolved in part by the general concept of stress-induced gene expression. As anticipated by Watson and Crick, their original dogma of *one gene—one protein—one structure—one function* was an oversimplification. A gene does not exist as one piece of DNA on a chromosome, which codes for one protein. Rather, each gene is a mixture of "exons" that code for parts of a protein, and "introns" that do not code for a protein. The introns, originally called "junk DNA" (before current research suggesting they have adaptive functions), must first be cut out and separated from the protein-coding exons. These exons are then "spliced" together to transcribe the gene into its messenger ribonucleic acid (mRNA), which will be translated into a protein that will regulate a physiological function.

It is currently estimated that about 30%-60% of the genes in the human genome can be spliced together in different ways to generate alternative sets of proteins that modulate physiological adaptation in response to challenge, stress, and trauma on many levels, ranging from the purely physical to the psychosocial.[6] It is not entirely clear, however, whether the use of the words, "adaptation, challenge, stress, and trauma" mean the same thing to molecular biologists and mind-body psychotherapists. Can the "oxidative stress" on a molecular level induced by physical trauma, for example, be equated with "psychosocial stress" and post-traumatic stress disorder (PTSD) in mind-body medicine? Can activities on the cognitive-emotional-behavioral levels of human experience really modulate the molecular pathways that lead to alternative gene expression in the brain and body in sickness and health? The "Cartesian divide" between mind and body is most obvious in the conceptual gap between genes and their biochemical pathways, on the one hand, and the apparently independent phenomenological activities of the mind and psychological experience, on the other. This paper extends the emerging field of *psychosocial genomics*[2,3,7-9] to include the concept of *stress-induced alternative gene expression* as an empirical and scientifically verifiable link between mind and body. The surprising idea that experiences on the psychological, social, and cultural levels can modulate gene expression on the molecular level is an unexpected validation of Selye's visionary concept of "the stress of life" for understanding the integration of mind and body in human nature. Psychosocial genomics now seeks to explore research paradigms that can demonstrate how psychotherapy and related cultural processes and rituals (such as meditation, prayer, and the deeply meaningful humanistic experiences of art, drama, dance, music, poetry, etc) can modulate alternative gene expression to facilitate health, rehabilitation, and healing.

PSYCHOSOCIAL STRESS ALTERS CHOLINERGIC GENE EXPRESSION

In this conceptual review, we will first outline the psychosocial genomics of stress-induced gene expression in the cholinergic system that mediates stimulation, excitation, and communication between the brain and the body. The cholinergic system consists of the acetylcholine gene, which codes for acetylcholine (the first neurotransmitter ever discovered) and its partner, the acetylcholinesterase gene, which codes for the enzyme that destroys (hydrolyzes) acetylcholine when it completes its job of excitatory neurotransmission in the central nervous system (at synapses connecting neurons). Also included in the cholinergic system is the peripheral nervous system (at neuromuscular junctions). Such pairs (and sometimes families) of genes, which turn physiological functions on and off in complex biofeedback loops of communication with the environment, are typical of the classical regulatory systems of body and mind involving neurotransmitters, hormones, the psychoimmune system, and growth factors of the brain and body.

In the past few decades, however, research teams led by the molecular biologist, Hermona Soreq, and others have discovered and investigated many nonclassical functions of the acetylcholinesterase gene induced by stress.[10-12] In essence, it has been found that a wide variety of stressors, ranging from the psychosocial (eg, crowding stress or the gentle handling of mice by humans), to the environmental (alternations in the circadian cycle), to the physical (forced swimming) and molecular (drug and chemical intoxication, as in the Gulf War syndrome) can lead to the overexpression of the acetylcholinesterase (AChE) gene to modulate a wide range of mind-body processes (see Figure 1).

The wide range of stress-associated pathologies associated with massive expression of the AChE gene (illustrated in Figure 1) denotes a convergent outcome of acute psychosocial stress, chemical intoxication, and traumatic head injury. Chronic stress and a long-term excess of AChE promotes cognitive decline and neurodeterioration, as in Alzheimer's disease,[13] Down's syndrome, and some symptoms of myasthenia gravis.[14] Age-related and late-onset dysfunctions that are particularly vulnerable to alternative splicing variations include age-related macular degeneration (AMD), amyotropic lateral sclerosis (ALS), and frontotemporal dementia with Parkinsonism.[15] Massive expression of the human AChE gene has been associated with autoimmune disorders such as Grave's dis-

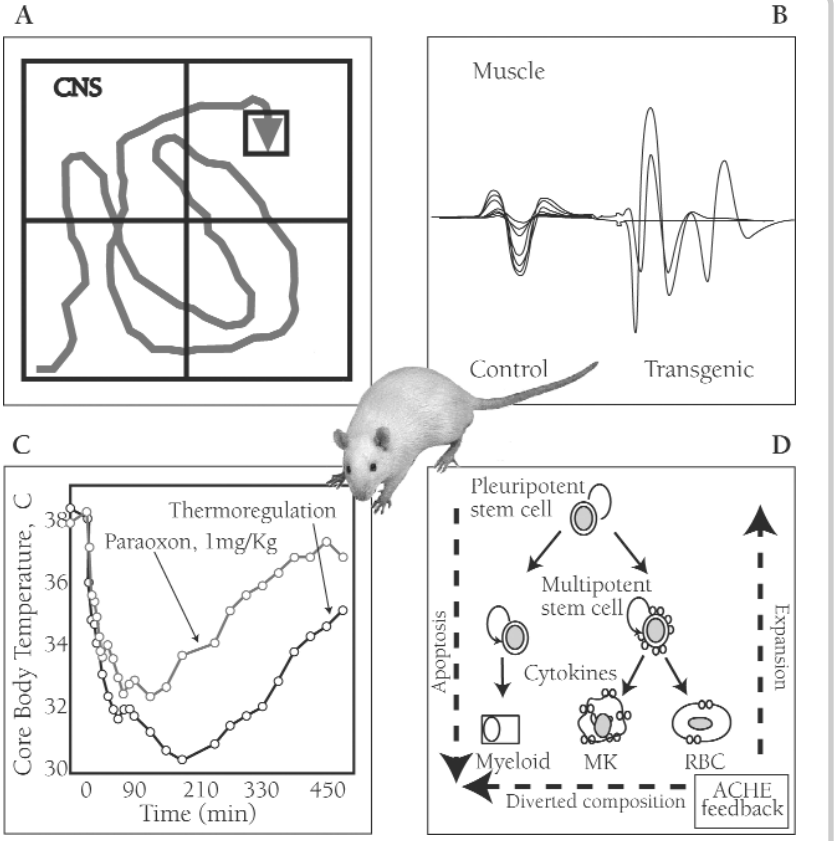

FIGURE 1 Stress-associated pathologies associated with overexpression of the AChE gene (* *see Figure Notes at end of article*)

ease, the leukemias,[10] ovarian carcinomas, thrombocytopenia, and exposure to organophosphate insecticides.[16] AChE activity has also been associated with meningioma, astrocytoma, and glioblastoma tumors.[17,18] In mice, the accumulation of stress-associated AChE predicts male infertility.[19] How such apparently divergent pathologies can be related has been investigated with more detailed investigations of the alternative splicing variants of the AChE gene produced by acute and chronic stress.

ACUTE AND CHRONIC STRESS INDUCE ALTERNATIVE GENE SPLICING

Acute and chronic stress can induce a series of changes in cholinergic gene expression (or "splicing") that alter the normal balance of acetylcholine and acetylcholinesterase metabolism associated with PTSD and many related mind-body dysfunctions[11] that are well summarized by Sternfeld, et al[13]:

> *Both chronic stress and acute stress promote neuroanatomic changes in brains of evolutionarily diverse species, including higher vertebrates and humans. Some of these changes likely reflect normal physiological adaptation to injury, environmental challenge, traumatic experience, or even standard maintenance conditions of laboratory animals. However, stress may also precipitate delayed or prolonged neuropsychiatric dysfunction, the etiology of which is yet poorly defined. For example, up to 30% of individuals exposed to an acute traumatic experience develop posttraumatic stress disorder, a syndrome characterized by progressively worsening personality disturbances and cognitive impairments. The cellular and molecular factors mediating the switch between physiological accommodation of stress and progressive disease are unknown but likely reflect complex interactions between the genetic background of the challenged individual and the nature of the stress insult. The accepted notion is that physiological stress responses are beneficial in the short run but detrimental if over-activated or prolonged. This concept suggests the existence of stress modulators designed to regulate the extent, duration, and long-term impact of acute stress responses. We recently reported massive induction of a unique mRNA species encoding the rare "read-through" variant of acetylcholinesterase (AChE-R) in the brains of mice subjected to forced swimming stress. AChE-R differs from the dominant "synaptic" variant, AChE-S, in the composition of its C-terminal sequence. . . In hippocampal brain slices, induced AChE-R seemed to play a role in delimiting a state of enhanced neuronal excitation observed after acute cholinergic stimulation. This observation suggested that AChE-R acts as a stress modulator in the mammalian brain (p. 8647). . . .Our current findings therefore demonstrate that AChE-R, most likely with another modulator or modulators, may be beneficial in the response to acute stress at two levels: (i) by dampening the acute cholinergic hyperactivation that accompanies stress, and (ii) by protecting the brain from entering a downward spiral into progressive neurodegeneration through an as-yet unidentified mechanism, which could involve noncatalytic activities and/or direct competition with AChE-S. In that case, the diversion of up-regulated AChE expression after insults to the central nervous system from production of the usual AChE-S to the unusual AChE-R isoform [by stress-induced alternative gene expression or splicing] would reflect an elegant evolu-*

tionary mechanism to avoid the dangers of over-expressed AChE-S. These findings imply that mutations conferring heritable up-regulation of AChE-R would protect the mammalian central nervous system from some age-dependent neuropathologies. The definitive role of AChE-R after transient stress or drug-induced overexpression remains to be examined in additional animal models permitting conditional regulation of AChE-R expression.

Figure 2 summarizes major feedback loops between AChE-S (synaptic AChE) and AChE-R (readthrough AChE) in what has been called "the vicious circle of stress and anticholinesterase responses."[20] AChE-S, the principle form of acetylcholinesterase, is found in the synapse where it regulates classical excitatory function of acetylcholine neurotransmission between neurons in the brain, mediating visual, motor, and emotional experiences in normal and highly aroused states of consciousness, as well as in REM dream sleep[21] and at the neuromuscular junctions in the body.[12] AChE-R (R is for *readthrough* because of the way it is spliced together), the second most common form of acetylcholinesterase, accumulates in the brain and the blood in response to acute psychological stress, as well as to toxins from the environment.[16]

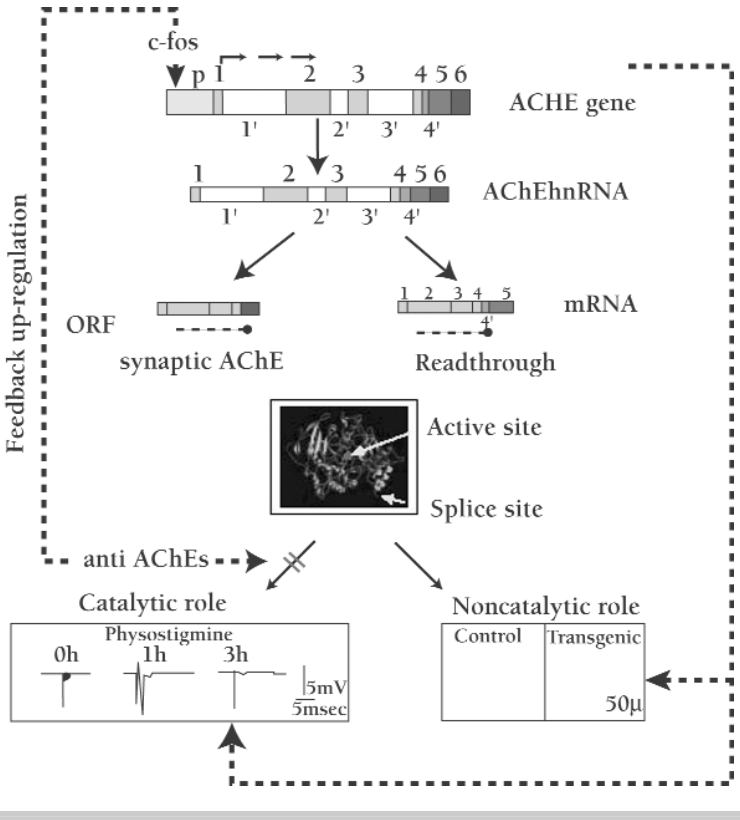

FIGURE 2 Major feedback loops between AChE-S (synaptic AChE) and AChE-R (readthrough AChE) († *see Figure Notes at end of article*)

In the next section, we will frame a number of open questions about the possible associations between the immediate-early gene, c-fos, stress-induced alternative gene expression (illustrated in Figure 2), and the psychosocial genomics of mind-body psychotherapy that are now ripe for experimental investigation.

THE PSYCHOSOCIAL GENOMICS OF MIND-BODY PSYCHOTHERAPY

In psychophysiology, the central role of the immediate-early genes, such as c-fos, has been described from at least 3 points of view: 1) a marker for neuronal activity and states of consciousness[22]; 2) a modulator of acute stress signals[20]; and 3) a mediator of mind-body communication and healing.[2,3] Levsky, et al,[23] illustrate the typical 90-120 minute activity cycle of c-fos and 10 other genes in what they call "Single-Cell Gene Expression Profiling."[23] A key goal of the Human Genome Project is to relate the expression of specific genes to the proteins they code for and the physiological pathways they regulate, often in response to environmental factors such as stress. Levsky, et al, summarize their work in this area:

The instantaneous transcriptional activity of genes in single cells allows observation of causes and effects of expression. Eventually, the physiological state of cells within tissues will become synonymous with a pattern of gene expression. This will provide a quantitative approach to factors influencing gene expression patterns, such as those that occur in cytopathology, development and cell differentiation, infectious disease, and response to drug treatment. Investigation of functional genomics may now be approached at the cellular level. We expect that the enormous information inherent to the expression of many genes in large-cell populations will aid the understanding of relationships among genes in single nuclei and their cooperative and cumulative roles in physiology and disease.

I would now like to present the case for extending the relationship between gene expression and the psychophysiology of Kleitman's[24] Basic Rest-Activity Cycle (BRAC), which has an identical 90-120 minute periodicity, to the psychosocial genomic foundations of the classical 4-stage creative process applied to mind-body medicine.[2,25]

The wave-like gene expression profile of *c-fos* over 120 minutes, described and illustrated by Levsky, et al, is strikingly similar to the wave-like profile of the 4-stage creative cycle of growth-oriented psychotherapy long

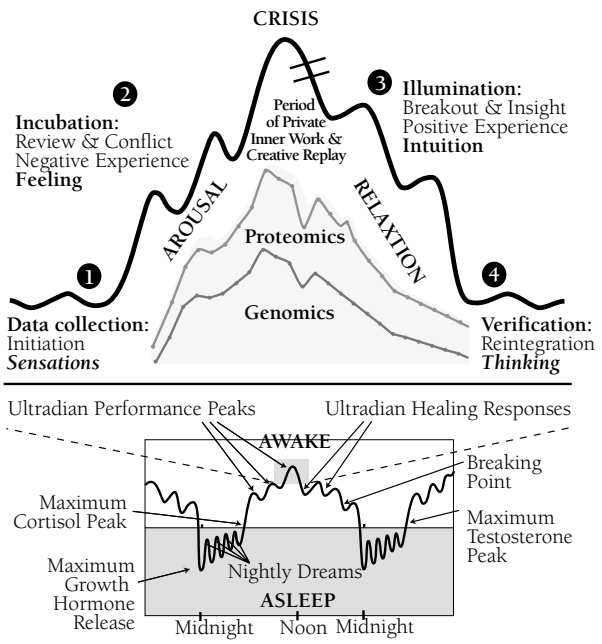

FIGURE 3 Rossi's bioinformatics 4-stage creative process
(‡ *see Figure Notes at end of article*)

known as the "Breakout Heuristic,"[2,25-28] which usually takes place over 90-120 minutes (see Figure 3).

At this point, we do not know whether the similarity between 1) the wave-like activity profile of the immediate-early gene, *c-fos* in its role in mediating the acute adaptive and chronic maladaptive dynamics of alternative cholinergic gene expression, and 2) the wave-like bioinformatics 4-stage creative cycle of psychotherapy (Figure 3) that emerges from the genomics and proteomics levels is simply a coincidental observation or a deeply meaningful psychobiological connection that is now ripe for more direct experimental investigation.[29] We can, however, summarize the open questions that need to be answered to establish the case for a causal, albeit complex, nonlinear association between alternative gene splicing and expression in psychotherapy and mind-body medicine.

Chronic Stress in Neurological, Autoimmune, and Age-Related Dysfunctions

The basic idea that the positive adaptive functions of brain plasticity can be facilitated by the initial excitatory cholinergic dynamics of acetylcholine in acute stress (while chronic stress overloads the CNS, endocrine, and immune systems to the point of dysfunction) now requires more direct documentation via gene expression profiling of AChE-S, AChE-E, and AChE-R throughout the entire 24-hour circadian cycle in normal and clinical populations. The shifts between dominance of AChE-S, AChE-E, and AChE-R may be a common denominator in the critical transitions between the initial positive adaptations of acute, but brief, stress to the pathologies associated with chronic stress, which are the mission of mind-body medicine to understand and heal.

Time Parameters of Stress, Gene Expression, and Psychotherapy

The hypothesized association between 1) the normative 90-120 minute profile of gene expression, 2) the cholinergic dynamics of the acute and chronic-stress response, 3) Kleitman's Basic-Rest Activity Cycle, and 4) the 4-stage creative response in mind-body psychotherapy now require direct investigation via coordinated studies with brain imaging and DNA micro-array technology.[2,30] Figure 3 shows how the first 2 stages of the creative process in psychotherapy evoke a state of psychobiological *arousal* that corresponds to the state of excitement of the CNS, mediated at least in part by the neurotransmitter acetylcholine. In the psychiatric literature of 100 years ago, this state of arousal sometimes led to an emotionally driven state of *conflict, negative emotions*, and *crisis* at the peak of stage 2, when a patient apparently lost emotional control in what was described as hysteria. Recently, emotionally driven re-experiencing and replays of fear and *conflict* behavior have been associated with stress-induced alternative splicing and AChE-R.[31] Depth psychotherapy began when this *crisis* was channeled into a therapeutic catharsis, evoking traumatic early memories that were the putative source of PTSD and "neuroticism" in the early work of Pierre Janet, Sigmund Freud, and others.[32,33] With a bit of luck and good guidance, this state of hyperarousal (acetylcholine excitation) sometimes led to a breakthrough to new insight, problem solving, positive psychological experience, and the resolution of stress-induced mind-body symptoms in stage 3 of the creative cycle. When the patient was encouraged to appreciate the value and meaning of this apparently spontaneous insight, the *crisis* was resolved, symptoms were reportedly healed, and *relaxation* was experienced in the second half of the creative cycle (stages 3 and 4 in Figure 3). While this psychobiological shift from arousal to crisis, insight, and symptom resolution with relaxation and a sense of well-being is characteristic of all modern cognitive-behavioral approaches to psychotherapy, its relationship to Kleitman's BRAC and the classical 4-stage creative process is rarely noted.[2,25]

In Figure 3, note the two small parallel lines indicating a break just after the peak or crisis between stages 2 and 3 of the creative cycle. This "break" indicates the unknown process by which the *arousal* of stages 1 and 2 was shifted to the *relaxation* of stages 3 and 4 of the creative process. It is now hypothesized that this break is mediated by alternative gene splicing, leading to a dominance of AChE-R over AChE-S, as summarized by Sternfeld, et al:

Our current findings therefore demonstrate that AChE-R, most likely with another modulator or modulators, may be beneficial in the response to acute stress at two levels: (i) by dampening the acute cholinergic hyperactivation that accompanies stress, and (ii) by protecting the brain from entering a downward spiral into progressive neurodegeneration through an as-yet unidentified mechanism, which could involve noncatalytic activities and/or direct competition with AChE-S.[13(p8652)]

We now need more direct tests of this psychobiological hypothesis of mind-body therapy through assessment of the time parameters of the relationships between AChE-S (more present in stages 1 and 2 of the creative cycle) and AChE-R (more evident in stages 3 and 4 of the creative cycle).

BRAIN PLASTICITY AND ALTERNATIVE GENE SPLICING IN THE CREATIVE CYCLE

Brain plasticity refers to the growth and transformations in the physical structure, connections, and functions of the cells of the brain, generally described as synaptogenesis[34] and neurogenesis[35] during 1) normal embryological development and the entire lifecycle, and during 2) the normal, everyday life changes in the neural networks associated with psychological experiences of novelty, creativity, significant memory, learning, and behavior. Acetylcholinesterase (AChE) is expressed during the embryological development of the brain, where it is involved in the growth of neurites, the extensions on the axons of neurons where the synapses are located.[10] In the well-functioning adult, the alternative splicing of the AChE gene is presumably involved in brain plasticity in regulating the classical excitatory functions of acetylcholine neurotransmission in mediating visual, motor, and emotional experiences in normal and highly aroused states of creative consciousness, as well as during REM dream-sleep.[21] We now need DNA micro-array studies of the relationships between the 3 alternative splicing variants of the acetylcholinesterase gene (AChE-S, AChE-R, and AChE-E) with working and declarative memory,[36] during the 4-stage creative process while awake during psychotherapy, as well as in the various states of sleep (particularly REM dream-sleep versus stage 4 deep-sleep) in normal and clinical populations throughout the entire lifecycle.

A recent example from mathematics illustrates the phenomenology of the 4-stage creative process,[37] which may correspond to the psychobiological dynamics of the growth of neurites and synaptogenesis in brain plasticity. I hypothesize that the shift from a dominance of AChE-S to AChE-R is manifest in this example during the emotional transition from the peak of creative excitation, conflict, and crisis (typical of the state of psychobiological arousal of stages 1 and 2) to the relaxation of stages 3 and 4 when the new creative insight is finally integrated and experienced as real.[2] Research on the cognitive and emotional aspects of relationship between *intuition* in stage 3 and *thinking* in stage 4 has been recognized by the 2002 Nobel Prize for Economics awarded to Daniel Kahneman.[38]

Upon first exposure, everything new seems to be unreal. A creative experience sometimes seem unreal precisely because it is still so new that it does not yet have a well-established place in our familiar contexts and ways of understanding. Those odd sensations and qualities of seeming distortion and grotesqueries in dreams are actually new patterns of awareness breaking through to consciousness as they shatter, reframe, and replace previous contexts and meanings in a seemingly spontaneous manner. That which seems absurd, bizarre, or meaningless in dreams only seems so from the older, more established attitudes and points of view that still dominate the conscious mind. Consider this poignant description of the initial sense of unreality and disbelief that mathematician Andrew Wiles experienced at the critical moment of correcting an error to finally solve a 300-year-old puzzle by proving Fermat's Last Theorem, as described by Aczel[37(p132-133)]:

Wiles studied the papers in front of him, concentrating very hard for about 20 minutes. And then he saw exactly why he was unable to make the system work. "It was the most important moment in my entire working life," he later said, describing the feeling. "Suddenly, totally unexpectedly, I had this incredible revelation. Nothing I'll ever do again will." At that moment tears welled up and Wiles was choking with emotion. What Wiles realized at that fateful moment was so indescribably beautiful, it was "so simple and so elegant—and I just stared in disbelief." Wiles walked around the department for several hours. [Acetylcholinesterase (AChE) accumulates in the hippocampus of the brain for several hours to modulate a peak in cholinergic hyperarousal.][20] He didn't know whether he was awake or dreaming. Every once in a while, he would return to his desk to see if his fantastic finding was still there—and it was.

Many similar experiences are reported by creative workers in literature and the arts.[39-41] Such creative moments are the basis of much art, drama, fantasy, and fiction in literature. What, for example, are the magical moments so common in fairytales and myth supposed to mean? Why do children, as well as adults, continue to find delight in reading such fictions? Well, you might respond that such delights are normal experiences of "enjoyment." What precisely is this positive experience in stage 3 of the creative process that we call enjoyment? We can understand why nature builds in the perception of

danger and the sensation of pain as an aid to survival, but what good is the enjoyment of the fictions of drama and tales of fantasy and wonder? I propose that the many experiences of so-called "enjoyment" on an explicit conscious level are aspects of the "numinosum." The *numinosum*, a word not found in most dictionaries, was created from Greek roots by the German scholar, Rudolph Otto,[42] to designate the common denominator of all spiritual experiences as a combined sense of fascination, mysteriousness, and tremendousness. Since C.G. Jung[43] adopted the word, *numinosum* to describe the major subjective experience of heightened human motivation and psychological transformation, I have generalized the numinosum to include the exciting feeling of a creative breakthrough moment in all the arts and sciences, as well as in psychotherapy.[2,3] I hypothesize that this experience of the numinosum is a deeply meaningful conscious experience that signals an unusually strong occurrence of gene expression, brain plasticity, and/or mind-body healing at an implicate or unconscious level. This is the essence of what I proposed as the "Novelty-Numinosum-Neurogenesis Effect," which is characteristic of experiences of mind-body healing.[2,3]

The Wide Range of Mind-Body Therapies and Cultural Rituals

We can now appreciate the broader and deeper implications of Hans Selye's vision when he wrote, "Perhaps the most fascinating aspect of medical *research on stress* is its *fundamentally permanent value to man*."[1(p304)] We need to investigate how stress-induced alternative splicing of the acetylcholinesterase gene and related psychosocial genomic systems may play a pivotal role in the deep psychobiology of the creative process in the arts and sciences, psychotherapy, meditation, and spiritual rituals.[44,45] This is also consistent with the experiencing of humanistic values such as compassion, beneficence, serenity, forgiveness, and gratitude that have been associated with mind-body medicine.[2] The receptivity of the neuroscience community to investigating the therapeutic potentials of such positive values associated with meditation, prayer, and spiritual practice, as well as psychotherapy, suggests progress will be made in this area of mind-body medicine in the immediate future[46,47] with DNA-array technology specialized for assessing alternative gene expression.

SUMMARY

The basic concept of psychosocial genomics—that psychological states, creative experience, social stressors, deeply meaningful cultural rituals, and values can modulate alternative gene expression and psychophysiology—is proposed here as an emerging scientific foundation for mind-body medicine and psychotherapy. Research documents how psychosocial stress can alter the expression of the acetylcholinesterase gene to generate 3 alternative proteins that are implicated in a wide variety of normal and adaptive mind-body functions, ranging from brain plasticity in acute but brief challenges, to the chronic stress and age-related pathologies of the central nervous, endocrine, and immune systems. We have extended the possible applications of stress-related alternative splicing of the acetylcholinesterase gene to the deep psychobiology of Kleitman's Basic Rest-Activity Cycle and the 4-stage creative process in brain plasticity, psychotherapy, and significant developments of human consciousness in the arts, sciences, and humanities. Consistent with Hans Selye's broad vision of the significance of stress in human experience, we outlined how positive humanistic values and cultural rituals generally associated with mind-body medicine may be investigated with current neuroscience methods of brain imaging and DNA micro-array technology.

Figure Notes

* Figure 1: Images of a wide range of the connections and consequences of stress-induced gene expression of acetylcholinesterase (AChE) in the cholinergic system of mind-body medicine. A. Overexpression of AChE in brain neurons results in cognitive impairments in the CNS as evident in failures in the Morris water maze. B. Progressive deterioration at the neuromuscular junction as evident in rapid fatigue in the electromyographic response. C. Failure in thermoregulation on exposure to drugs such as paraoxon. D. Enhanced expansion of multipotent stem cells in the blood (primary hematopoistic cells) and diversion of their differentiation toward myeloid lineages. (With permission from Soreq & Glick, 2000.)[16]

† Figure 2: An outline of the vicious biofeedback circle of stress and anticholinesterase responses. Psychosocial stress, physical head trauma, and chemical intoxication use a similar biofeedback loop (dashed lines) in which the up-regulation of the immediate-early gene, c-fos induces transcription of the acetylcholinesterase gene (AChE) by binding to its promoter (p). Alternative gene splicing takes place when AChE hnRNA (nascent heteronuclear RNA) is preferentially processed (heavy arrow) into AChE-R mRNA (readthrough) that can protect the CNS from hyperactivity and neurodeterioration via overactivated AChE-S (synaptic AChE). Open reading frames (ORF) of the alternatively spliced genes (AChE-S & AChE-R) that are eventually translated into a protein with physiological functions are shown as short dashed lines with a dot. In its catalytic role AChE modulates acetylcholine availability and cholinergic excitation that may have survival value in acute short-term life emergencies. Exposure to anticholinesterases (such as physostigmine) increases acetylcholine levels increasing cholinergic excitation in the hippocampus of the brain. Within 3 hours, there is a delayed suppression of this initial excitation (downward right broken arrow) due to trauma and stress. The noncatalytic role of AChE modulates the growth of neurites (the extensions on the dendrites of neurons where synapses are located). In transgenic mice (where a gene is inserted experimentally), in comparison with controls, the overexpression of AChE, however, attenuates dendritic branching on brain neurons, which results in a deterioration of memory, learning, and behavior due to the accumulation of excess AChE in this vicious circular biofeedback response. A third form of the acetylcholinesterase gene, AChE-E (erythrocyte AChE), that can arise from alternative splicing associated with a range of physiological functions and pathologies of the blood and bone is not illustrated here. (With permission from Kaufer, et al, 1999.)[20]

‡ Figure 3: The Bioinformatics of the 4-stage Creative Cycle in Mind-Body Psychotherapy. The lower diagram summarizes the normal circadian (~ 24 hours) profile of alternating 90–120 minute ultradian (less than 20 hours) rhythms of waking and sleeping characteristic of Kleitman's Basic Rest-Activity Cycle (BRAC) for an entire day in a simplified manner. The ascending peaks of rapid eye movement (REM) sleep typical of nightly dreams every 90–120 minutes or so are illustrated along with the more variable ultradian rhythms of activity, adaptation, and rest in the daytime. This lower figure also illustrates how many hormonal messenger molecules of the endocrine system such as growth hormone, the activating and stress hormone, cortisol and the sexual hormone testosterone, have typical circadian peaks at different times of the 24-hour cycle.[48,49]

The upper diagram outlines my hypothesized basic psychobiological unit of psychotherapy as the creative utilization of one natural 90–120 minute ultradian rhythm of arousal and relaxation, which is illustrated here as the classical 4 stages of the creative process: 1) Data collection; 2) Incubation; 3) Illumination; 4) Verification that has been well documented by Wallas[50] and others.[51] In general, the 4 basic psychological functions of sensations, feeling, intuition, and thinking as originally described by Jung[52] appear to be related to the 4 stages of the creative process.[2,3]

I hypothesize that this classical 4-stage creative process emerges from the proteomics (protein) level illustrated by the middle curve depicting the energy landscape for protein folding into the correct structures needed for psychobiological functioning (adapted and redrawn from Cheung, et al).[53] This proteomic level is, in turn, emergent from the genomics level illustrated by the curve below it (adapted from Levsky, et al).[23] This genomics curve represents the actual gene expression profiles of the immediate-early gene c-fos and 10 other genes (alleles) over the typical ultradian time period of 90-120 minutes. All genes showed measurable activation within 5 or 10 minutes. By 40 minutes, a peak of activation was reached, and by 90-120 minutes gene expression had returned to the baseline.

This set of curves illustrates our basic psychosocial genomics hypothesis: gene expression (genomics) and the dynamics of proteins (proteomics) are the ultimate bioinformatics foundation of the classical 4-stage creative process in psychotherapy and mind-body medicine. These biological transformations at the genomics and proteomics levels are typically experienced as Kleitman's 90-120 minute Basic Rest-Activity Cycle in normal human psychophysiological rhythms. The basic psychosocial genomics hypothesis implies that these psychobiological rhythms can be entrained and utilized to modulate the genomics and proteomics levels for therapeutic purposes by many of the diverse and seemingly unrelated approaches of mind-body medicine.[2,3,7,8,9,26,28,54,55]

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