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Epigenetic Remodeling of Delta FosB Protein: Its Role in Regulation of Stress

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Abstract

Stress is not affected only on brain but also on the other parts of body like changes in heart rate, blood pressure levels, circadian rhythm etc. Recent studies have been established that exposure to stress promotes alterations in several epigenetic characters like histone acetylation and methylation as well as DNA methylation, in various limbic brain regions. Chromatin remodeling processes are necessary for learning and memory. However, abnormal epigenetic modifications can lead to cognitive deficits. DeltaFosB (ΔFosB) is protein of Fos family. FosB gene forms FosB and ΔFosB as product. Increased expression of FosB over ΔFosB in nucleus accumbens (NAc) region of brain protects animals from the deleterious effects of chronic stress. Moreover, epigenetically, H3K9me2 is enriched at the FosB promoter in NAc of human depressed patients. FosB has very low life while ΔFosB has exceptionally long life span. Thus persists for long time in the stress condition and leads to depression and anxiety. It has also been revealed that elevation in ΔFosB level occurs due to chronic stress condition. The epigenetic factors responsible for stress are governed by ΔFosB expression level. The expression of ΔFosB in turn depends on the presence of serum response factor (SRF) transcription factor. SRF transcription factor is encoded by srf gene. To understand the mechanism of stress condition, srf gene can be one of the promising targets to uncover the problems related to stress conditions.

Keywords: Stress; Epigenetic; ΔFosb; Srf Gene; Fosb; Chromatin Remodeling

Abbreviations: SRF: Serum Response Factor; Nac: Nucleus Accumbens; PTSD: Post-Traumatic Stress Disorder; HPA: Hypothalamic-Pituitary-Adrenal; BDNF: Brain Derived Neurotrophic Factor; TPA: Tissue Plasminogen Activator; CRF: Corticotrophin Releasing Factor; Ecb: Endocannabinoids; FAAH: Fatty Acid Aminohydrolase; GR: Glucocorticoid Receptor; ERK: Extracellular Signal-Regulated Kinase; MAPK: Mitogen-Activated Protein Kinase; HDAC: Histone Deacetylase; AD: Alzheimer's disease; HMTs: Histone Methyltransferases; SAM: S-adenosylmethionine.

Introduction

Stress is not always what it seems to be. Stress can be divided into three categories: good stress; tolerable stress

and toxic stress. Early life stress can alter neural architecture thus can lead to toxic stress, development of psychopathologies such as post-traumatic stress disorder and depression [1,2]. There is a strong inter-individual variability in susceptibility to stress. Most of the individuals remain resilient: they can maintain normal physiological and psychological functions despite being subjected to horrendous stress [3,4]. Stress does not occur due to any single reason. A lot of factors are responsible for the stress condition. It can be genetic or epigenetic factors. In this increasing technological world, the standard of living of a person defines its mental and social health along with the physical health. Increasing work pressure adversely affects the health condition and leading cause of stress in humans.

Chronic stress refers to intense traumatic events like accidents, physical assault, sexual assault, natural disasters, or combat exposure, leading to psychopathologies such as complex post-traumatic stress disorder (PTSD) or non-traumatic but major events in life, whereby an individual is exposed to sustained periods of stress, for example, care giving, difficult divorce, or a stressful work environment leading to burnout [2].

The brain is the central organ for processing and adapting to various social and physical stresses, as it is the organ that stores memories, regulate physiological and behavioral responses and determines what is threatening for the body [5]. The thought of a stressful situation activates many neuronal circuits, particularly hypothalamic-pituitary-adrenal axis (HPA axis), the locus coeruleus and autonomic noradrenergic centers in the brain stem [6,7].

Various mediators that help to adapt to stress include: cell surface mediators, cytoskeletal mediators, epigenetic regulation and non-genomic mechanisms [8]. Exposures to multiple stressors and dysregulation of the non-linear interactions lead to wear and tear of the body and the brain. This is termed as allostatic load and overload [5,9]. Allostasis is the active process of adapting to stressors via mediators such as cortisol and autonomic, metabolic and immune system that act together in a non-linear fashion to maintain homeostasis [10].

The effect of stress is not only on brain but also on the other body parts like changes in heart rate, blood pressure levels, circadian rhythm etc. Chromatin remodeling processes are necessary for learning and memory. Abnormal epigenetic modifications can lead to cognitive deficits. Moreover, it has been observed in various studies that exposure to stress promotes alterations in various epigenetic marks; in particular, histone acetylation and methylation as well as DNA methylation, in various limbic brain regions.

There are Some Molecules that are Necessary/Permissive for Remodeling

a) Brain derived neurotrophic factor (BDNF): It is a facilitator of plasticity and growth. BDNF overexpression blocks effects of chronic stress. BDNF haplo insufficiency prevents stress induced plasticity [11,12].
b) Tissue plasminogen activator (tPA): It is a secreted signaling molecule and protease. It is required for stress-induced spine loss in hippocampus and medial amygdala. It is required for acute stress-induced increase in anxiety. Corticotrophin releasing factor (CRF) is responsible for activating tPA. CRF in amygdala regulates tPA release [13,14].
c) Corticotrophin releasing factor (CRF): It is secreted in hippocampus by interneurons. It downregulates thin spines via RhoA signaling [14,15].
d) Lipocalin-2: It gets activated at the time of acute stress. It downregulates mushroom spines. Lipocalin-2 KO increases neuronal excitability and anxiety [16,17].
e) Endocannabinoids (eCB): It gets induced via glucocorticoids. It regulates emotionality and HPA habituation and shut off.

CB1 receptor KO increases anxiety and basolateral amygdala dendrite length and causes stress like retraction of prefrontal cortical dendrites, likely through the regulation of glutamateric transmission.

Fatty acid aminohydrolase (FAAH) is a key regulator of eCB action [18-20].

Stressors Alter Gene Expression Via Following Mechanisms

a) Direct effect of glucocorticoids on gene transcription
b) Activation of epigenetic mechanisms involving histone modification and methylation/hydroxyl-methylation of CpG residues in DNA [21,22].

Epigenetic Mechanism behind the Stress Condition

Many genes that get altered after glucocorticoid and chronic stress exposure in the hippocampus are known as epigenetic regulators [23]. For example; social defeat stress in rodents showed changes in both histone

methylation and acetylation. The mechanism underlying this includes: Glucocorticoid, via glucocorticoid receptor (GR), facilitates signaling of extracellular signal-regulated kinase (ERK)-mitogen-activated protein kinase (MAPK) (ERK-MAPK) pathway to downstream mitogen and stress-activated protein kinase-1(MSK-1) and ElK-1.The activation of this pathway results in serine 10(S10) phosphorylation and lysine 14(K14) acetylation at histone H3 i.e.H3S10p-K14ac. This leads to induction of immediate early genes, c-Fos and Erg-1 [24,25]. Epigenetically, H3K9me2 is enriched at the FosB promoter in NAc of human depressed patients. Expression of a construct containing a transcriptionally repressive domain (Fosb-ZFP-G9a) decreased FosB expression and increased the level of the repressive histone modification H3K9me2 [26]. It has also shown that expression of Fosb-ZFP-G9a increased depression-like behavior in a chronic social defeat stress model, indicating that the H3K9me2 modification mediates this effect [26]. Increased expression of FosB over ΔFosB in nucleus accumbens region of brain protects animals from the deleterious effects of chronic stress [26].

Vialou, et al. have used bitransgenic mice that inducibly overexpress ΔFosB specifically in the adult NAc and dorsal striatum to test the functional consequences of ΔFosB induction. These mice have shown a reduced propensity to develop social avoidance after four or ten days of social defeat (Figure 1) [27].

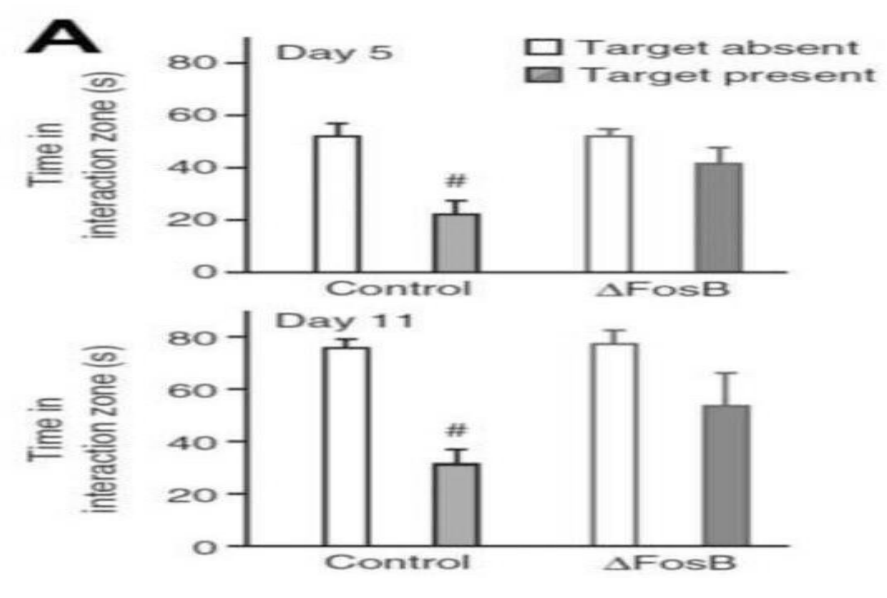

Figure 1: ΔFosB induction in nucleus accumbens (NAc) region by chronic social defeat stress mediates resilence. Inducible bitransgenic mice over expressing ΔFosB in D1type MSNs do not develop the social aversion, which is a hallmark of social defeat stress after either 4or 10days of defeat with mice tested on days 5 or 11, respectively [27].

Corbett, et al. demonstrated that spontaneous seizures increase expression of ΔFosB, a highly stable Fos-family transcription factor, in the hippocampus of an Alzheimer's disease (AD) mouse model [28]. ΔFosB suppressed expression of the immediate early gene c-Fos, which is critical for plasticity and cognition, by binding its promoter and triggering histone deacetylation. Acute histone deacetylase (HDAC) inhibition or inhibition of ΔFosB activity restored c-Fos induction and improved cognition in AD mice. Administration of seizure inducing agents to nontransgenic mice also resulted in ΔFosB-mediated suppression of c-Fos, suggesting that this mechanism is not confined to AD mice. These results explain observations that c-Fos expression increases after acute neuronal activity but decreases with chronic activity.

The Fos family proteins heterodimerize with Jun family proteins (c-Jun, JunB or JunD) to form active activator protein-1 (AP-1) transcription factors that bind to AP-1 sites, which is present in the promoters of certain genes to regulate their transcription. These Fos family proteins

are induced rapidly and transiently in specific brain regions after acute administration of many drugs of abuse [29]. Very different responses have been observed after chronic administration of drugs of abuse (Figure 2).

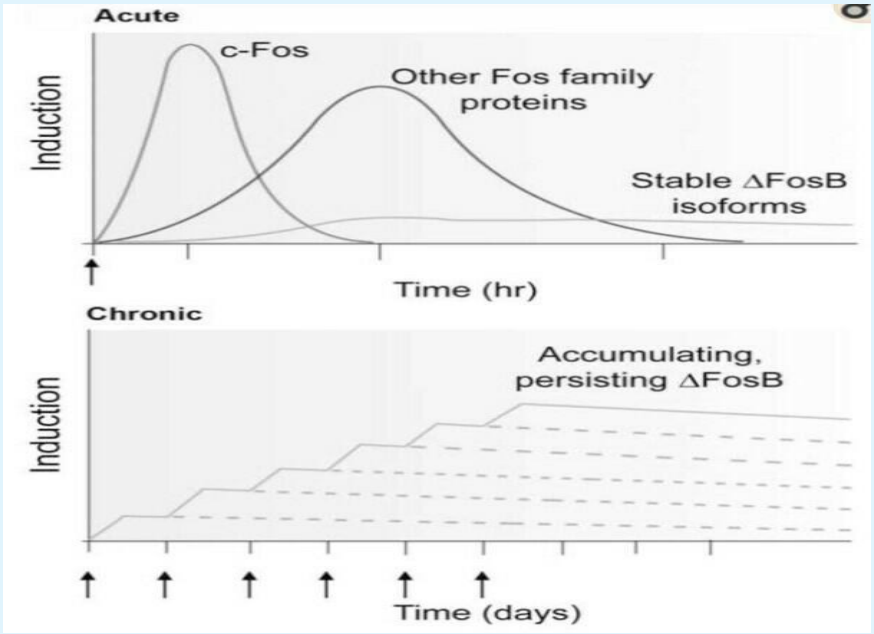

Figure 2: Scheme showing the gradual accumulation of ΔFosB versus the rapid and transient induction of other Fos family proteins in response to stress or another stimulus [29].

FosB gene forms FosB and ΔFosB as product. ΔFosB is protein of Fos family. These FosB have very low life while ΔFosB has exceptionally long life span. Thus persist for long time in the stress condition and leads to depression and anxiety.

Two mechanisms are responsible for the stability of ΔFosB:

a) ΔFosB has a deletion of 2degron domains at the C terminal as compared to FosB. One of the domain targets FosB for ubiquitylation and degradation in proteosome and the other targets FosB degradation by an ubiquitin and proteasome independent manner (Figure 3).
b) ΔFosB is phosphorylated by several protein kinases at its N-terminal, which stabilizes the protein.

Earlier it was noticed that ΔFosB gets activated due to alcohol consumption but the mechanism was not clear. Pauli, et al. [30] identified different patterns of FosB/DeltaFosB expression during withdrawal between EtOH_High and EtOH_Low groups [30]. They also showed that behavioral variability observed in acquisition phase of ethanol induced locomotor sensitization is accompanied by distinct neuronal plasticity during withdrawal period. In addition, their results suggested that different patterns of FosB/Delta FosB expression detected in sensitized and non-sensitized mice were more related to withdrawal period rather than to the chronic drug exposure, probably due to the tolerance of drug-induced FosB/DeltaFosB transcription.

It has also been discovered that elevation in ΔFosB level occurs due to chronic stress condition. Decreasing the expression of ΔFosB or increasing the level of FosB can help in relieving from stress. ΔFosB is produced due to activation of serum response factor (SRF) that is coded by the gene Srf gene.

ΔFosB is unique in that it accumulates in response to repeated stimulation due to its unusual protein stability [31].

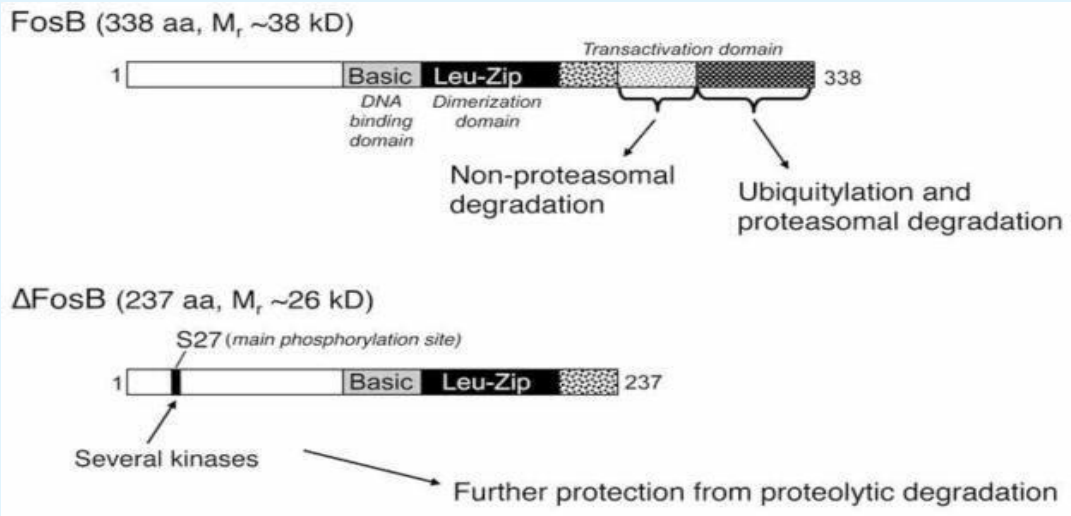

Figure 3: Biochemical basis of ΔFosB's unique stability. ΔFosB is formed by deletion of some portion of FosB as shown in the figure, which provides the unique stability to ΔFosB [29].

Epigenetics

Epigenetics is the mechanism that regulates genomic information by chemical modifications to DNA and histones that can alter cell and tissue specific patterns of gene expression [32,2]. These reversible modifications of DNA and chromatin structure mediate the interaction of the genome with a variety of environmental factors and generate changes in the pattern of gene expression in response to these factors [32]. An epigenetic trait is a stable, mitotically and meiotically heritable phenotype that results from changes in the pattern of gene expression without alterations of the DNA sequence [32].

Epigenetic mechanisms

A. DNA Methylation:

Methylation of cytosine residue at 5'position results in projection of methyl group into the major groove ofDNA [33]. In mammals, this predominantly occurs in the palindromic sequence 5'-CpG-3'. The location of CpG bases in mammalian DNA occurs at high concentration in some specific regions called CpG islands.

CpG methylation in promoter region generally represses transcription of genes.DNA methylation is catalysed by DNA methyltransferases (DNMTs) [34]. DNMTs can directly interact with transcription factors, performing the methylation of promoter region at specific locations. Nearly 80 transcription factors are found to be associated with DNMTs [35].

B. Histone Modifications:

In case of eukaryotes DNA is packed densely into chromatin through interactions with large protein complexes, nucleosomes. Nucleosome core is composed of histone octamer. The N-terminal tails of histones exhibit multiple, reversible covalent modifications. These alter the accessibility of DNA to the transcriptional machinery in a regulated fashion [36].

a) **Acetylation:** Histone acetylation (Figure 4) negates positive charge of lysine residue in histone tail. It is associated with transcriptional activation [37,38]. Histones are acetylated by histone acetyltransferases (HATs). HATs use acetyl coenzyme A as a cosubstrate. Deacetylation occurs by histone deacetylases (HDACs). HATs acetylate multiple lysine residues in the tails of both H3 and H4 [36].

b) **Methylation:** Histone methylation (Figure 4) is linked with both transcriptional repression and activation depending on the residue being methylated and the extent of methylation. Both arginine residues can be methylated. Methylation occurs by histone methyltransferases (HMTs). It uses S-adenosylmethionine (SAM) as a co substrate [39].

c) Many other modifications of histone tails include phosphorylation (Figure 4), ubiquitination, sumoylation and ADP ribosylation etc [36].

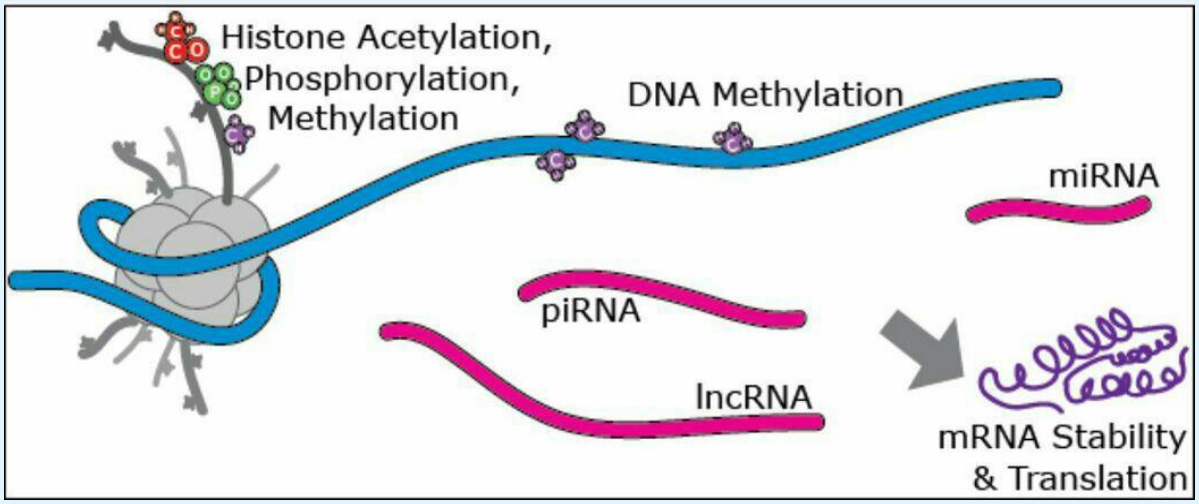

Figure 4: Molecular epigenetic modifications. Histone modifications like acetylation, methylation, phosphorylation etc and the non-coding RNA and the DNA itself convey the epigenetic information and coordination between DNA and transcription and chromatin modification machinery (Adapted from Griffiths, et al.)[40,8].

C. Non Coding RNAs

Many types of ncRNAs are well known, such as ribosomal (rRNA) and transfer (tRNA) RNA, lncRNAs and various short varieties, including micro (miRNA), small nuclear (snoRNA), promoter associated small RNAs (PASR), Piwi-interacting RNA (piRNA), and transcription initiation (tiRNA) types [36].

Antidepressants

The use of antidepressant drugs used till date are generally increasing the level of stress response hormones such as cortisol, norepinephrine, adrenocorticotropic hormone, endorphins etc. thus leading to relieve from stress.

However many associated drawbacks have been seen related to antidepressant action:

1. They work in too few people i.e. response rates within 6-8weeks are around 70% while resubmission rates are sometimes considerably lower.
2. It takes too long until the work i.e. the patients have to wait sometimes more than 2 months, until they get markedly better.
3. Despite substantial improvement among new antidepressants, they still have too many side effects like tiredness, restlessness, sexual dysfunction, weight gain and in some cases even aggressiveness [41].

The effects of the epigenetic modifications of FosB and Delta FosB, are summarized in table 1.

Epigenetic modifications	FosB	DeltaFosB
Histone 3 (H3) Acetylation	Lysine 14 acetylation	-
Effects	Modulate drug and stress evoked behavior and gene expression [42].	-
Methylation	H3K9me2	Lysine 9 methylation
Effects	H3K9me2 enrichment at *FosB* is suppressed in the NAc by repeated cocaine dose and it also increased at *FosB* in the NAc of depressed humans. Local overexpression or knockdown of G9a in NAc potently controls drug and stress responses in rodent [43].	The role of histone methylation changes at c-Fos and Egr-1 immediate-early genes (IEGs) is still unclear [42].

Table 1: Effects of epigenetic modifications of Fos B and Delta Fos B.

Conclusion and Future Directions

The epigenetic factors responsible for stress are governed by ΔFosB expression level. The expression of ΔFosB in turn depends on the presence of SRF transcription factor. SRF transcription factor is encoded by srf gene. On knocking out the srf gene, ΔFosB would not get formed thus epigenetic cause of stress can be eliminated. Moreover the epigenetic modification i.e. H3K9me2 can be altered back to H3S10p-K14ac epigenetic modification [8].This epigenetic-editing approach, with assessments of physiological changes in gene expression, uncovers clear differences in the stress-induced phenotypes by Fosb gene manipulation. Such targets may be used to help initiative to develop antidepressant drug in future years. Ultimately, studies of ΔFosB elucidate the ways in which it is possible to elaborate detailed transcriptional mechanisms of stress and anti-stress action. Recent study demonstrated a molecular mechanism by which epileptic form activity might contribute to cognitive deficits in Alzheimer's disease and epilepsy. This mechanism highlights seizure-induced ΔFosB as a transcription factor that critically regulates hippocampal memory [2]. We propose that through the use of CRISPR-Cas9 technology, N-terminal of ΔFosB in human can be modified. The novel mechanistic understanding may provide new insight into improved treatments of stress.

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