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A Neurochemical Basis for an Epigenetic Vision of Psychiatric Disorders (1996-2009)

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1. Introduction

In 1996, Dr. Costa was invited by Prof. Boris Astrachan, Chairman of the Department of Psychiatry at the University of Illinois at Chicago, to direct the research of the “Psychiatric Institute, Department of Psychiatry, School of Medicine, at the University of Illinois at Chicago.” He was asked to develop a seminal research program on psychiatric disorders. Viewed in retrospect, Dr. Costa met and surpassed the challenge, as was usual for him.

To elucidate the molecular mechanisms whereby nurture (epigenetic factors) and nature (genetic factors) interact to cause major psychiatric disorders was at the center of Dr. Costa's mission for the last 15 years of his research at the Psychiatric Institute.

The challenge for Dr. Costa and his colleagues (Auta, Caruncho, Davis, Grayson, Guidotti, Impagnatiello, Kiedrowski, Larson, Manev, Pappas, Pesold, Pinna, Sharma, Smalheiser, Sugaya, Tueting, Veldic [1-11]) had always been to find new ways to prevent and treat psychiatric disorders with pharmacological agents that failed to have major unwanted side effects.

A fundamental barrier to new drug development for the treatment of major psychiatric disorders was and still is now an incomplete understanding of the etiopathogenetic mechanisms underlying the symptomatology of these diseases.

2. GABAergic dysfunction in schizophrenia (SZ)

From the start, Dr. Costa was aware of the importance of GABAergic transmission in maintaining an efficient synchronization of cortical activity and also that the reciprocal

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interaction between GABAergic interneurons and glutamatergic pyramidal neurons was disrupted in the cortex and hippocampus of SZ patients.

Between 1998 (Impagnatiello et al. [17]) and 2000 (Guidotti et al. [32]), Dr. Costa's laboratory reported that a GABAergic neuropathology is detected in the hippocampus and cortex in the postmortem brains of SZ and BP disorder patients. This GABAergic neuropathology is characterized by a decrease in the expression of GAD₆₇ mRNA and protein and by a decreased expression of reelin mRNA and protein.

Reelin is a large (400 kDa) extracellular matrix protein that we discovered to be most abundantly synthesized in GABAergic neurons (Pesold et al. [19], Caruncho et al. [11], Guidotti et al. [32], Costa et al. [34], Lacor et al. [29], Liu et al. [36], Veldic et al. [87], Ruzicka et al. [86]). Upon secretion, reelin adheres to postsynaptic densities located on dendritic spines and on shafts of pyramidal neurons (Liu et al. [36], Costa et al. [34]).

In these early experiments, it was proved that reelin harmonizes local dendritic protein synthesis rates necessary for: 1) dendritic spine formation, 2) spine maturation, and 3) the regulation of glutamate receptors structure and function (Costa et al. [34], Guidotti et al. [100], Tueting et al. [1999], Dong et al. [51]).

Based on these discoveries, it was concluded that a GABAergic neuropathology dominated by a decrease of GAD₆₇ and reelin could explain the disturbances of the reciprocal interaction between GABAergic and glutamatergic neurons that likely underlies the appearance of the positive and negative symptoms and cognitive dysfunctions seen in psychotic patients (Guidotti et al. [67], Costa et al. [88,99], Grayson et al. [71,79], Dong et al. [103]).

In Dr. Costa's laboratory, Tueting and colleagues [22,83] and Carboni et al. [60] tested this hypothesis using heterozygous reeler mice that express phenotypic characteristics typical of SZ patients. They also proved that the GABAergic dysfunction in these mice was reverted by imidazenil, a benzodiazepine analogue discovered by Dr. Costa in 1985, which has high affinity and intrinsic activity for α_2 , α_3 , α_5 GABA_A receptors subunits but is devoid of action at α_1 -containing GABA_A receptors (Costa et al. [42], Guidotti et al. [67]). Imidazenil fails to produce sedation or tolerance and therefore is a good candidate drug to treat psychotic symptoms and cognitive deficits in SZ.

3. Evidence supporting a role of epigenetic factors in psychosis

The next question was “what is the cause of GABAergic neurotransmitter downregulation in prefrontal cortex of SZ and BP patients?” This question was addressed by Dr. Costa and his colleagues in a seminal paper entitled “Reelin and schizophrenia: a disease at the interface of the genome and the epigenome” (Costa et al. [42]).

A first clue to this puzzle came when Grayson and coworkers showed that the reelin gene is regulated by drugs that open chromatin in the vicinity of the promoter (Chen et al. [45]). This suggested that reelin was regulated epigenetically through changes in DNA methylation. Secondly, in support of a role for aberrant epigenetic mechanisms in the

pathogenesis of SZ and BP disorder, Dr. Costa and colleagues (Costa et al.[88], Ruzicka et al. [86], Veldic et al. [56,65,87], Zhubi et al. [102]) reported that the downregulation of GAD₆₇ or reelin expression in GABAergic neurons of SZ and BP patients is associated with an overexpression of DNA methyltransferase 1 (DNMT1) and DNA methyltransferase 3a (DNMT3a) in layers I and II of BA9, BA10, and BA17. However, this overexpression is not seen in layers V and VI or in the striatum of BP disorder patients (Veldic et al. [87]). DNMTs belong to a family of enzymes that catalyze the transfer of a methyl group from the methyl donor S-adenosylmethionine (SAM) to the 5' carbon of cytosines embedded in cytosine phosphodiester guanine (CpG) islands of many gene promoters. Although increased promoter methylation induced by the overexpression of DNMTs in SZ and BP disorder patients may be the cause of the downregulation of GABAergic genes, the inhibitory action of DNMTs on gene expression may also occur through the formation of repressor complexes. These chromatin complexes often contain other specific proteins (e.g., methyl CpG binding domain proteins, SIN3A, and histone deacetylases) that repress transcription via a modification of chromatin structure, shifting chromatin from a permissive (open) conformation to a repressive (closed) conformation (Chen et al. [45], Costa et al. [88], Dong et al. [75], Grayson et al. [79], Kundakovic et al. [85]).

In addition to the increased expression of DNMT1 and DNMT3a, which is associated with decreased reelin and GAD₆₇ expression in a selected population of GABAergic interneurons of the prefrontal cortex (PFC), the hypothesis that an epigenetic pathology of GABAergic promoters is operative in the transcriptional downregulation of several genes in SZ or BP disorder patients is supported by evidence of 1) increased S-adenosyl-methionine (SAM) in the PFC (Guidotti et al. [84]), 2) hypermethylation of cytosines in CpG islands of reelin (Grayson et al.[71,79]) and other selected promoters and the associated downregulation of mRNA expression in the PFC of psychotic patients, and 3) increased histone deacetylase expression in the PFC (Sharma et al. [72]).

Furthermore, support for the hypothesis that an epigenetic chromatin remodeling pathology contributes to the downregulation of GABAergic or glutamatergic genes in psychotic patients is indirectly supported by clinical studies conducted in the early 1970s (for review see Wyatt RJ, Termini BA, Davis J. Schizophr Bull 4:1-44, 1971). Methionine (MET), the precursor of SAM (the universal methyl donor utilized by DNMTs to methylate cytosines in CpG islands), administered in large doses (10-20 g/day) for 3-4 weeks to SZ patients was reported to exacerbate psychotic symptomatology. Following this lead, scientists at the Psychiatric Institute showed that in both the mouse FC and in neuronal cultures, the administration of large doses of MET induces an increase in SAM and the hypermethylation of selective CpG-rich GABAergic promoters, including GAD₆₇ and reelin. MET also facilitates the downregulation of their expression (Chen et al. [45], Noh et al. [69], Mitchell et al. [68], Tremolizzo et al. [48,66]). Importantly, brain levels of GAD₆₅ and that of other housekeeping genes are not affected (Tremolizzo et al. [48]).

4. DNA promoter methylation patterns in neurons constitute a dynamic process

It was thought that in neurons, DNA methylation patterns were established during early development and remained stable thereafter. However, there is increasing evidence supporting the concept that in adult neurons, methylation patterns of specific cytosine/guanine (CpG) dinucleotide-rich promoters change rapidly.

Studies by Tremolizzo, Tueting, Dong, Grayson, and Guidotti suggest that treating mice protractedly with MET to induce reelin and GAD₆₇ promoter hypermethylation results in a behavioral, neuroanatomical, and biochemical epigenetic mouse model of SZ (Tremolizzo et al. [48,66], Dong et al.[89], Tueting et al. [105]. However if MET is withdrawn, reelin and GAD₆₇ promoter hypermethylation decreases by ~50% after the seventh day and returns to control levels after 12-14 days of MET withdrawal (Dong et al. [89,93]).

Collectively, these data challenge the classic concept that DNA 5-mC patterns remain stable in postmitotic cells and strongly suggest that by increasing SAM brain content, MET facilitates promoter methylation mediated by DNMT1 or DNMT3a in the CNS. Unlike the DNA sequence of a cell, which is stable and strongly conserved, epigenetic processes are highly dynamic; they can be tissue-specific, developmentally-regulated, and modified by exposure to a range of drugs or environmental factors (for reviews see Ptak C, Petronis A. *Ann Rev Pharmacol Toxicol* 48:257-76, 2008 and Szyf M. *Biochemistry (Mosc)* 70:533-44, 2005).

5. Valproate (VPA) and other histone deacetylase (HDAC) inhibitors promote chromatin remodeling, induce DNA-demethylation, and regulate cognitive function

The dynamic nature of the epigenome means that, unlike pathogenic DNA sequence mutations, epigenetic disruptions are potentially reversible and thus a realistic target for pharmacological intervention, similar to what was reported regarding the regulation of reelin by methylation. Similar studies showed that GAD₆₇ promoter expression is regulated by changes in methylation. HDAC inhibitors activate mRNA expression and decrease promoter methylation (Chen et al. [45]).

In psychiatry, the use of VPA as a drug that enhances GABAergic transmission is based on the observation that protracted VPA treatment in rodents induces an increase of GAD₆₇ and reelin expression (Tremolizzo et al. [48]). Recent studies from our group and others suggest that GAD₆₇ and reelin are increased by VPA because this drug not only inhibits HDACs and modifies the “histone code” but also decreases methylated sites at reelin and GAD₆₇ promoters (Dong et al. [89], Kundakovic et al. [85], Chen et al. [45]), thus preventing the recruitment of corepressor protein complexes.

Studies by Dong et al. [89, 103], Simonini et al. [76], and Tremolizzo et al. [48] have shown that if HDAC inhibitors such as VPA and the benzamide derivative MS-275 are given to

mice after MET withdrawal, they dramatically accelerate reelin and GAD₆₇ promoter demethylation during the subsequent 24-48 hours.

VPA's ability to facilitate the demethylation of reelin and GAD₆₇ promoters was not caused by a direct inhibitory action of this drug on DNMT1 or DNMT3a expression or DNMT activity or on an inhibitory action of VPA on SAM biosynthesis (Dong et al. [93]). These data are in line with the idea that HDAC inhibitors trigger an active DNA demethylation process that may be associated with an increase of histone acetylation (Kundakovic et al. [85], Chen et al. [45]). Since the biochemical identity of the catalytic process mediating DNA demethylation in mammalian cells remains unclear, one cannot conclude that the accelerated reelin and GAD₆₇ promoter demethylation elicited by HDAC inhibitors in the mouse FC result from a direct induction of a DNA demethylase activity, nor is the result of an indirect recruitment or activation of a preexisting demethylation mechanism related to histone code remodeling. Experiments are now being conducted in our laboratory (Drs. Gavin and Matrisciano) to address these questions.

Evidence has been obtained in rodents that MET-induced reelin and GAD₆₇ promoter hypermethylation can be prevented or effectively reversed by VPA and other HDAC inhibitors (Dong et al. [89], Tremolizzo et al. [66], Simonini et al. [76]) in the absence of any action on DNMT. This supports the concept that a putative DNA-demethylase activity may also play a pivotal role in regulating the appropriate dynamic balance of DNA cytosine-5 methylation patterns in the mammalian brain.

Cortical histone acetylation and DNA demethylation has been implicated in cognitive function (Tremolizzo et al. [66], Tueting et al. [105]). Taken together, these data suggest that pan-HDAC inhibitors such as VPA and other more selective chromatin remodeling agents may provide a potential adjuvant treatment for the cognitive deficits present in SZ and BP disorder patients or in other neuropsychiatric disorders.

6. Epigenetic processes can be a target of antipsychotic drug action

To address the issue of whether antipsychotic drugs acting on epigenetic mechanisms alter DNA methylation of GABAergic gene promoters, experiments were carried out in Swiss albino mice treated with typical and atypical antipsychotics, including haloperidol, clozapine, olanzapine, quetiapine, and risperidone. Dr. Dong and colleagues found that reelin and GAD₆₇ promoters were significantly demethylated in the FC of mice receiving three days of treatment with clinically relevant doses of clozapine and relatively high doses of quetiapine and olanzapine but not in mice receiving haloperidol or risperidone (Dong et al. [93]).

Results similar to those in the FC were obtained in the striatum, which expresses an almost homogeneous population (~90%) of GABAergic medium spiny neurons that also synthesize reelin (Dong et al. [93]). Because in the same mice, reelin promoter methylation in the liver fails to change, it was inferred that clozapine and congeners modify methylation in the CNS and specifically in GABAergic neurons. Importantly, the action of clozapine on GABAergic promoter demethylation appears to be independent of an inhibitory effect on DNMT (Satta et al. [95]).

In the same study, it was found that the administration of clozapine but not that of haloperidol, in parallel with the increase of DNA demethylation, induces increased nuclear H3 hyperacetylation at reelin or GAD₆₇ promoters in the FC (Dong et al. [93]). It is conceivable that antipsychotics that induce chromatin remodeling act by increasing histone acetylation, thereby recruiting putative DNA demethylating enzymes. This would convert chromatin at specific loci from an inactive/silenced state to an active/state positively modulating synaptic plasticity and regulating cognitive function (for a review see Guidotti et al. [100]).

The precise mechanism whereby clozapine modulates the histone code and induces DNA-demethylation in GABAergic neurons remains to be elucidated. However, clozapine is marginally active by itself and we found it difficult to reconcile the structure of clozapine with that of any other currently known HDAC inhibitor.

7. Effect of VPA and clozapine co-administration on DNA-demethylation

Important for the translational implications, the DNA-demethylating actions of clozapine, olanzapine, and quetiapine were synergistically potentiated by the co-administration of a threshold HDAC inhibitory dose of VPA (Dong et al. [93,103]). Furthermore, the administration of clozapine (5 mg/kg s.c./three days/twice a day) in conjunction with VPA (70 mg/kg s.c./three days/twice a day) reverses the downregulation of GAD₆₇ expression induced in mice by seven days of MET administration, suggesting an epigenetic action of this drug combination through histone acetylation and promoter demethylation (Guidotti et al. [110]).

In mammalian cells, active DNA-demethylation is achieved, at least in part, by a base-excision repair pathway that first requires the conversion of 5-methyl cytosine (5mC) to thymine (T) through deamination (for a review see Zhu JK. Ann. Rev Genet 43:143-66, 2009). It has been proposed that coupling between 5mC deaminase and G/T mismatch DNA glycosylase is favored by the presence of “growth arrest and DNA-damage-inducible protein 45” (Gadd45) α and β . These are small active nuclear acidic proteins that are induced in neurons by stress or by drugs that increase neuronal activity (Guidotti et al. [110]).

Given our data suggesting that subtypes of antipsychotic medications and VPA can synergistically interact to activate DNA-demethylation, Dr. Matrisciano and Dr. Gavin examined the possibility that VPA and antipsychotic drugs elicit functionally-relevant DNA-demethylation changes altering the expression or activity of Gadd45 α or β . They found that in the FC of mice that had been given 70 mg/kg of VPA/three days/twice a day, Gadd45 β mRNA expression is increased compared to vehicle-treated controls. Histochemical studies with specific Gadd45 β antibodies also show that cortical pyramidal neurons of mice treated with VPA (70 mg/kg/three days) exhibit increased nuclear Gadd45 β expression compared with vehicle-treated mice. Moreover clozapine, in a dose that per se increases Gadd45 β , potentiates the action of VPA. Since these doses of clozapine and VPA induce promoter-demethylation, taken together, the data suggest that in addition to DNMTs, neuronal promoter methylation can be regulated by the activity of a putative DNA demethylase, which can remove a methyl group from the carbon 5 of C. Hence evidence suggests that in

neurons, promoter methylation is a dynamic process that can be altered in response to environmental factors such as stress, drugs, and various psychopathologies.

Presently, the overarching goal of the studies inspired by the pioneer work of Dr. Costa is to develop a classification of antipsychotic drugs based on their action on chromatin remodeling and DNA demethylation in GABAergic neurons. However, the biochemical identity and function of the process mediating DNA demethylation in mammalian cells requires further clarification (see reviews by Szyf and Zhu).

8. Concluding remarks

The pioneering research on psychosis and the breakthroughs in the study of aberrant epigenetic molecular mechanisms operative in SZ and BP disorder represent another example of Dr. Costa's prodigious output of important discoveries during the 60 years of his productive career. Dr. Costa pursued science with relentless intensity and was enormously productive. He was never interested in the safe predictable regions of the scientific arena; he was always at the edge and he was always provocative. It is striking how consistently innovative he was!

Dr. Costa left us not only with the rich legacy of his work in Neuroscience but also with many talented students and postdocs he trained.

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