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HDAC2 as a new target to improve schizophrenia treatment

Mitsumasa Kurita,
Department of Psychiatry, Mount Sinai School of Medicine, New York, NY 10029, USA

Terrell Holloway, and
Department of Psychiatry, Mount Sinai School of Medicine, New York, NY 10029, USA

Javier González-Maeso
Departments of Psychiatry, Neurology and Friedman Brain Institute, Mount Sinai School of Medicine, New York, NY 10029, USA

Javier González-Maeso: Javier.Maeso@mssm.edu

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One of the main characteristics of treatment of psychiatric disorders, such as schizophrenia and depression, is the chronic administration (weeks, months or even years) of therapeutic compounds. A recent study suggests the existence of a compensatory mechanism through which neurons in the cerebral frontal cortex adjust the balance between two signaling pathways in response to chronic treatment with atypical antipsychotic drugs [1]. The ability of the system to maintain its dynamic equilibrium involves epigenetic changes in chromatin structure that may ultimately restrain the therapeutic efficacy of schizophrenia treatment.

All life forms (microorganisms, plants and animals) function, reproduce and grow in an environment where conditions are often changing rapidly and unpredictably. However, to stay alive, the biological processes inside an organism need to remain mostly unchanged despite outside events. Survival depends on the ability of an organism to maintain a dynamic equilibrium (or homeostasis) between its internal and external environments [2]. Failure to respond adequately may result in disease, malfunction or death. There is growing evidence that epigenetics (the study of heritable modifications that regulate gene expression without alterations in the underlying DNA sequences) may play an essential role in the cellular events that facilitate the adaptation of an individual cell to its environment [3]. With this background, it is reasonable to speculate that some of the epigenetic changes induced by chronic administration of therapeutic drugs may be considered by the organism as external factors to reverse or compensate.

Correspondence to: Javier González-Maeso, Javier.Maeso@mssm.edu.

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Schizophrenia is a neuropsychiatric condition that affects more than one percent or the population worldwide [4]. The rates of schizophrenia are similar across populations and apparently uncorrelated with socioeconomic status or cultural background. Diagnostic features of schizophrenia include positive symptoms, such as hallucinations and delusions, as well as negative symptoms, such as inability to pay attention and social withdrawal. Treatment with either typical (e.g., chlorpromazine and haloperidol) or atypical (e.g., clozapine, olanzapine and risperidone) antipsychotics often results in substantial improvement or even remission of hallucinations and delusions. However, a fifth to a third of schizophrenic patients do not respond to antipsychotic medication, and will continue to experience psychosis and other positive symptoms in spite of the treatment [5]. Deficits in attention and memory function are also present in the majority of schizophrenic patients. Importantly, clinical studies suggest that these cognitive impairments show minimal improvement or exacerbations after treatment with atypical antipsychotic drugs [6], a conclusion that has been further supported by rodent models of memory formation [7]. Previous findings convincingly demonstrate that chronic treatment is involved in some of the mechanisms underlying the therapeutic effects of antipsychotic drugs, such as changes in gene expression that affect synaptic plasticity [8]. However, it is a logical assumption that, together with these molecular routes that are necessary for therapeutic action, chronic administration of antipsychotic drugs will also give rise to signaling pathways through which neurons and other cells compensate the changes caused by the treatment itself.

The neurotransmitter serotonin plays an important role in the neurochemical alterations responsible for schizophrenia and other psychotic disorders [9]. Second generation (or atypical) anti-psychotic drugs bind with high affinity and block the function of the serotonin 5-HT_{2A} and other monoaminergic receptors [10]. Psychedelic drugs, such as lysergic acid diethylamide (LSD) and psilocybin, activate 5-HT_{2A} receptor-dependent signaling pathways [11], and induce alterations in cognition and perception that share similarities with some of the symptoms in schizophrenic patients [12]. Together, these findings suggest that the 5-HT_{2A} receptor may be at least in part responsible for psychotic symptoms in schizophrenia patients. The glutamatergic system in general, and the metabotropic glutamate 2 (mGlu2) receptor in particular, profoundly affect cellular signaling, electrophysiological and behavioral responses that require expression of the 5-HT_{2A} receptor in cortical pyramidal neurons [13]. In particular, drugs that activate mGlu2 receptors indirectly repress the psychosis-like states induced by psychedelics in rodent models. It has also been shown that 5-HT_{2A} and mGlu2 receptors modulate the function of signaling pathways that exert opposite effects on psychosis and antipsychotic-like behaviors [14, 15]. This functional crosstalk between 5-HT_{2A} and mGlu2 receptors may provide the basis for the explanation of the findings obtained in mouse and human frontal cortex after chronic treatment with atypical antipsychotic drugs [1].

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The fundamental structural entity of chromatin is the nucleo-some [3]. Each nucleosome consists of approximately two turns of DNA wrapped around an octamer of histone proteins (H2A, H2B, H3 and H4). Histone deacetylases (HDACs) represent a large family of epigenetic regulators that compact chromatin structure and repress gene transcription through the removal of acetyl groups from histone tails. It has been recently shown that chronic treatment with clozapine and risperidone, but not with the typical antipsychotic haloperidol, decreases the density of 5-HT_{2A} receptor in frontal cortical regions [1, 14]. This effect of chronic atypical antipsychotic drugs on 5-HT_{2A} receptor density has been implicated as one of the mechanisms responsible for their antipsychotic effects. However, chronic treatment with clozapine or risperidone also induces repressive histone

modifications at the promoter region of the *mGlu2* gene (also known as *GRM2*) through a mechanism that involves 5-HT_{2A} receptor-dependent modulation of the promoter activity of the histone deacetylase 2 gene [1]. Thus, the effect of chronic treatment with clozapine on 5-HT_{2A} receptor density was accompanied by increased expression and binding of HDAC2 to the *mGlu2* promoter, findings that provide a molecular explanation for the decreased acetylation of histone H3 at the *mGlu2* promoter in postmortem frontal cortex of treated, but not untreated, schizophrenic subjects [1]. This pattern of repressive histone modifications induced at the promoter region of the *mGlu2* gene by chronic atypical antipsychotic treatment also correlates with *mGlu2* mRNA expression. Since, as described above, mGlu2 receptor-dependent signaling pathways have been shown to oppose the cellular effects induced by activation of the 5-HT_{2A} receptor, together, these findings suggest a compensatory mechanism as a possible explanation for the 5-HT_{2A} receptor-dependent effect of chronic treatment with atypical antipsychotic drugs on *mGlu2* expression.

> "…adjunctive treatment with the HDAC inhibitor SAHA prevented the repressive histone modifications induced at the *mGlu2* promoter by chronic treatment with clozapine, and significantly improved its antipsychotic-like behavioral effects in mouse models of psychosis and cognitive deficits."

The next question was whether reduction of these HDAC2-dependent effects induced by chronic treatment with atypical antipsychotic drugs at the *mGlu2* promoter would improve their clinical efficacy. Notably, adjunctive treatment with the HDAC inhibitor SAHA (suberoylanilide hydroxamic acid) prevented the repressive histone modifications induced at the *mGlu2* promoter by chronic treatment with clozapine, and significantly improved its antipsychotic-like behavioral effects in mouse models of psychosis and cognitive deficits [1]. The hypothesis that inhibition of HDAC2 may represent a new therapeutic target for the treatment of schizophrenia is supported by previous clinical trials. Thus, some, but not all, of the studies showed that valproate (one of the functions of which is to act as a nonspecific HDAC inhibitor) improves the clinical efficacy of atypical antipsychotic drugs, including clozapine, risperidone and olanzapine [16–20]. However, the design of compounds that specifically inhibit HDAC2 is definitely needed in order to validate their therapeutic use in preclinical and clinical assays.

From a more general perspective, these findings suggest the presence of neuronal mechanisms that maintain a dynamic equilibrium in response to external stimuli, and provide the basis for further investigation into the limited therapeutic efficacy of drugs that are administered chronically to treat psychiatric disorders, including schizophrenia, depression, and bipolar disorder.

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Biographies

References

1. Kurita M, Holloway T, García-Bea A, et al. HDAC2 regulates atypical antipsychotic responses through the modulation of *mGlu2* promoter activity. Nat. Neurosci. 2012; 15(9):1245–1254. [PubMed: 22864611]
2. Marder E. Neuromodulation of neuronal circuits: back to the future. Neuron. 2012; 76(1):1–11. [PubMed: 23040802]
3. Borrelli E, Nestler EJ, Allis CD, Sassone-Corsi P. Decoding the epigenetic language of neuronal plasticity. Neuron. 2008; 60(6):961–974. [PubMed: 19109904]
4. Dobbs D. Schizophrenia: the making of a troubled mind. Nature. 2010; 468(7321):154–156. [PubMed: 21068803]
5. Lieberman JA, Stroup TS, McEvoy JP, et al. Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N. Engl. J. Med. 2005; 353(12):1209–1223. [PubMed: 16172203]
6. Goldberg TE, Greenberg RD, Griffin SJ, et al. The effect of clozapine on cognition and psychiatric symptoms in patients with schizophrenia. Br. J. Psychiatry. 1993; 162:43–48. [PubMed: 8425138]
7. Addy N, Levin ED. Nicotine interactions with haloperidol, clozapine and risperidone and working memory function in rats. Neuropsychopharmacology. 2002; 27(4):534–541. [PubMed: 12377390]
8. Dong E, Nelson M, Grayson DR, Costa E, Guidotti A. Clozapine and sulpiride but not haloperidol or olanzapine activate brain DNA demethylation. Proc. Natl Acad. Sci. USA. 2008; 105(36):13614–13619. [PubMed: 18757738]
9. Geyer MA, Vollenweider FX. Serotonin research: contributions to understanding psychoses. Trends Pharmacol. Sci. 2008; 29(9):445–453. [PubMed: 19086254]
10. Miyamoto S, Miyake N, Jarskog LF, Fleischhacker WW, Lieberman JA. Pharmacological treatment of schizophrenia: a critical review of the pharmacology and clinical effects of current and future therapeutic agents. Mol. Psychiatry. 2012; 17(12):1206–1227. [PubMed: 22584864]
11. González-Maeso J, Weisstaub NV, Zhou M, et al. Hallucinogens recruit specific cortical 5-HT$_{(2A)}$ receptor-mediated signaling pathways to affect behavior. Neuron. 2007; 53(3):439–452. [PubMed: 17270739]
12. Vollenweider FX, Vollenweider-Scherpenhuyzen MF, Bäbler A, Vogel H, Hell D. Psilocybin induces schizophrenialike psychosis in humans via a serotonin-2 agonist action. Neuroreport. 1998; 9(17):3897–3902. [PubMed: 9875725]
13. Moreno JL, Sealfon SC, González-Maeso J. Group II metabotropic glutamate receptors and schizophrenia. Cell. Mol. Life Sci. 2009; 66(23):3777–3785. [PubMed: 19707855]
14. González-Maeso J, Ang RL, Yuen T, et al. Identification of a serotonin/glutamate receptor complex implicated in psychosis. Nature. 2008; 452(7183):93–97. [PubMed: 18297054]
15. Fribourg M, Moreno JL, Holloway T, et al. Decoding the signaling of a GPCR heteromeric complex reveals a unifying mechanism of action of antipsychotic drugs. Cell. 2011; 147(5):1011–1023. [PubMed: 22118459]

16. Casey DE, Daniel DG, Tamminga C, et al. Divalproex ER combined with olanzapine or risperidone for treatment of acute exacerbations of schizophrenia. Neuropsychopharmacology. 2009; 34(5):1330–1338. [PubMed: 19052541]
17. Citrome L, Casey DE, Daniel DG, Wozniak P, Kochan LD, Tracy KA. Adjunctive divalproex and hostility among patients with schizophrenia receiving olanzapine or risperidone. Psychiatr. Serv. 2004; 55(3):290–294. [PubMed: 15001730]
18. Meltzer HY, Bonaccorso S, Bobo WV, Chen Y, Jayathilake K. A 12-month randomized, open-label study of the metabolic effects of olanzapine and risperidone in psychotic patients: influence of valproic acid augmentation. J. Clin. Psychiatry. 2011; 72(12):1602–1610. [PubMed: 21813074]
19. Suzuki T, Uchida H, Takeuchi H, et al. Augmentation of atypical antipsychotics with valproic acid. An open-label study for most difficult patients with schizophrenia. Hum. Psychopharmacol. 2009; 24(8):628–638. [PubMed: 19946935]
20. Kelly DL, Conley RR, Feldman S, Yu Y, McMahon RP, Richardson CM. Adjunct divalproex or lithium to clozapine in treatment-resistant schizophrenia. Psychiatr. Q. 2006; 77(1):81–95. [PubMed: 16397757]