

D-Cell Hypothesis: Pathogenesis of Mesolimbic Dopamine Hyperactivity of Schizophrenia

Keiko Ikemoto^{1,2}

¹Department of Neuropsychiatry, Fukushima Medical University, School of Medicine, Fukushima, Japan

²Department of Psychiatry, Iwaki Kyoritsu General Hospital, Iwaki, Japan

Email: ikemoto@fmu.ac.jp

Received February 10, 2012; revised March 28, 2012; accepted April 24, 2012

ABSTRACT

In the present article, the author proposes a new “D-cell hypothesis” for mesolimbic dopamine (DA) hyperactivity of schizophrenia, of which relevant molecular mechanism has not yet been known. The “D-cell” is defined as “the non-monoaminergic aromatic L-amino acid decarboxylase (AADC)-containing cell”. The D-cell contains AADC but not dopaminergic nor serotonergic. D-cells produce trace amines, and also take up amine precursors and convert them to amines by decarboxylation. The author reported “dopa-decarboxylating neurons specific to the human striatum”, that is, “D-neurons” in the human striatum, and preliminarily the number reduction of D-neurons in the striatum and nucleus accumbens of postmortem brains of patients with schizophrenia. Trace amine-associated receptor, type 1 (TAAR1), a subtype of trace amine receptors, having a large number of ligands, including tyramine, β -phenylethylamine (PEA), and methamphetamine, is a target receptor for the latest neuroleptic discovery. Recent studies have shown that the decreased stimulation of TAAR1 on cell membranes or nerve terminals of DA neurons in the midbrain ventral tegmental area (VTA) increased firing frequency of VTA DA neurons. In brains of schizophrenia, dysfunction of neural stem cells in the subventricular zone of lateral ventricle may cause reduction of the number of D-neurons in the striatum and nucleus accumbens, and may result in decrease of trace amine synthesis. The decrease of stimulation of TAAR1 on terminals of VTA DA neurons caused by trace amine reduction may increase firing frequency of VTA DA neurons, and may finally cause mesolimbic DA hyperactivity. This innovative theory, “D-cell hypothesis” might explain mesolimbic DA hyperactivity in pathogenesis of schizophrenia.

Keywords: Dopamine; D-Neuron; Ventral Tegmental Area; Schizophrenia; TAAR1

1. Introduction

Schizophrenia is a mental illness, which afflicts approximately 1% of populations in the world, and manifests delusion, hallucination, disorganized thought, flattened affect, and impaired cognitive processes. Dopamine (DA) dysfunction [1,2], glutamate dysfunction [3,4], or neurodevelopmental deficits [5-8] are hypotheses for etiology of schizophrenia. DA dysfunction hypothesis suggests that mesolimbic DA hyperactivity causes positive symptoms such as paranoid-hallucinatory state of schizophrenia [1,2]. It is also explained by the efficacy of DA D2 blocker for paranoid-hallucinatory state, and also by hallucinogenic acts of DA stimulants, including methamphetamine or amphetamine [1,2]. Glutamate dysfunction theory was induced by the fact that intake of phencyclidine (CPC), an antagonist of NMDA receptor, produced equivalent to negative symptoms of schizophrenia, such as withdrawal or flattened affect, as well as positive symptoms [3,4]. The neurodevelopmental deficits hypothesis implicates that schizophrenia is the con-

sequence of prenatal abnormalities resulting from the interaction of genetic and environmental factors [5-8].

Mesolimbic DA hyperactivity [1,2], though frequently mentioned, the molecular basis of which has not yet been clarified. In the present article, the author proposes a new “D-cell hypothesis” for mesolimbic DA hyperactivity of schizophrenia, in which decrease of so-called D-cells in the striatum and nucleus accumbens [9] is involved.

2. What is “D-cell”

So-called “D-cells” were described, by Jaeger *et al.* [10] in 1983, in the rat central nervous system, and were defined “non-monoaminergic aromatic L-amino acid decarboxylase (AADC)-containing cells” [10]. D-cells contain AADC but not dopaminergic nor serotonergic [10]. D-cells produce trace amines [11,12], and may also act as an APUD (amine precursor uptake and decarboxylation) system that takes up amine precursors and converts them to amines by decarboxylation [13]. The localizations of D-cells were specified into 14 groups, from D1 (the spi-

nal cord) to D14 (the bed nucleus of stria terminalis), in rostro-caudal orders of the rat central nervous system, using AADC immunohistochemistry [14,15]. In this usage of a classification term, “D” means decarboxylation [4]. In rodents [13,16,17], a small number of D-cells in the striatum were rostrally described and confirmed to be neurons by electron-microscopic observation [13].

The author reported in 1997, “dopa-decarboxylating neurons specific to the human striatum [18-21]”, that is, “D-neurons” in the human striatum [20,22] (classified to be D15) [20], and later in 2003, and the number reduction of D-neurons in the striatum and nucleus accumbens of patients with schizophrenia [9,22].

3. Trace Amine-Associated Receptor 1 (TAAR1)

Cloning of trace amine receptors in 2001 [23,24], elicited enormous efforts for exploring signal transduction of these G-protein coupled receptors located on chromosome focus 6q23.1 [25]. The receptors are shown to colocalize with dopamine or adrenaline transporters in monoamine neurons, and to modulate the functions of monoamines [26-28].

The trace amine-receptor, type 1 (TAAR1) has a quite number of ligands, including tyramine, β -phenylethylamine (PEA), octopamine, and psychostimulants, for example, metamphetamine, 3,4-methylenedioxymethamphetamine (MDMA) and lysergic acid diethylamide (LSD) [23,25,29] (**Table 1**), and is now a target receptor for exploring novel neuroleptics [30,31]. TAAR1 knockout mice showed schizophrenia-like behaviors, with a deficit in prepulse inhibition [32]. TAAR1 knockout mice showed greater locomotor response to amphetamine and released more DA (and noradrenaline) in response to amphetamine than wild type mice [32].

It was clarified that signal increase to TAAR1 receptors on cell membranes of DA neurons in the midbrain ventral tegmental area (VTA) reduces firing frequency of VTA DA neurons [30-32].

Table 1. Ligands of trace amine-associated receptor, type 1 (TAAR1).

	Ligands of trace amine-associated receptor, type 1 (TAAR1)
Trace amines	Tyramine, beta-phenylethylamine (PEA)
Other amines	d- and l-amphetamine, methamphetamine
	3,4-methylenedioxymethamphetamine (MDMA) 3-iodothyronamine (TIAM)
Catecholamine metabolites	3-methoxytyramine(3-MT) 4-methoxytyramine (4-MT)
	Normetanephrine, metanephrine
DAT blocker	Nomifensine
DA agonists	Apomorphine, bromocriptine
Hallucinogen	Lysergic acid diethylamide (LSD)

4. The Novel Theory of Schizophrenia, “D-Cell Hypothesis”

The novel theory, “D-cell hypothesis” for explaining mesolimbic DA hyperactivity in pathogenesis of schizophrenia is shown in **Figure 1**. In brains of patients with schizophrenia, the number of D-neurons reduced in the striatum and nucleus accumbens [9], and this might cause the decrease of amounts of trace amines though the direct evidences have not yet been shown. The decrease of striatal D-neurons may be due to dysfunction of neural stem cells in the subventricular zone of lateral ventricle, as previously described [33,34]. Enlargement of the lateral ventricle [35,36], a usual finding documented in brain imaging studies of schizophrenia, may also be due to dysfunction of neural stem cells of the subventricular zone [33,34].

The decrease of TAAR1 stimulation on VTA DA neurons increased the firing frequency of VTA DA neurons [30,32]. This mechanism, which has recently been explored using animal models [30,32], may cause mesolimbic DA hyperactivity.

DA hyperactivity in the striatum [1,2] might also inhibit forebrain neural stem cell proliferation, as Kippen *et al.* [37] showed, and may lead additional decrease of D-neurons, which may induce additional hyperactivity of mesolimbic DA system. Actions of D2 blocking agents in pharmacotherapy of schizophrenia might partially be explained by the decrease of inhibition to forebrain neural stem cell proliferations. It might be consistent with the clinical experiences that D2 blocker is effective for treatment of schizophrenia.

5. Conclusion

So-called D-cells, as trace amine-producing cells, might be a clue for elucidating pathogenesis of DA hyperactivity of schizophrenia. Further exploration of signal transduction of D-cells is essential.

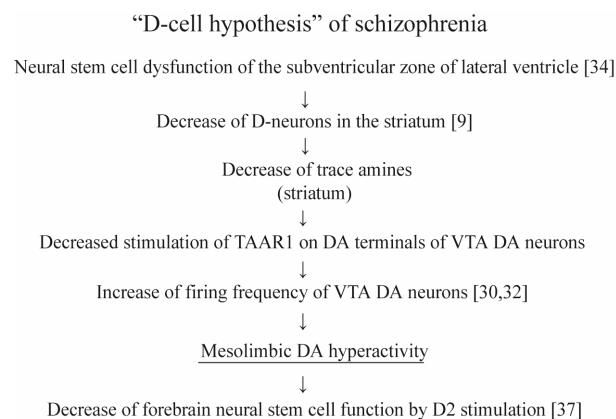


Figure 1. Schema of “D-cell hypothesis” of schizophrenia.

6. Acknowledgements

The present study was supported by Grant-in-Aid for Scientific Research from Japan Society for the Promotion of Science (C-22591265).

REFERENCES

- [1] T. Hokfelt, A. Ljungdahl, K. Fuxe and N. Takashima, "Dopamine Nerve Terminals in the Rat Limbic Cortex: Aspects of the Dopamine Hypothesis of Schizophrenia," *Science*, Vol. 184, No. 4133, 1974, pp. 177-179. [doi:10.1126/science.184.4133.177](https://doi.org/10.1126/science.184.4133.177)
- [2] M. Toru, T. Nishikawa, N. Mataga and N. Takashima, "Dopamine Metabolism Increases in Post-Mortem Schizophrenic Basal Ganglia," *Journal of Neural Transmission*, Vol. 54, No. 3-4, 1982, pp. 181-191. [doi:10.1007/BF01254928](https://doi.org/10.1007/BF01254928)
- [3] L. Watis, S. H. Chen, H. C. Chua, S. A. Chong and K. Sim, "Glutamatergic Abnormalities of the Thalamus in Schizophrenia: A Systematic Review," *Journal of Neural Transmission*, Vol. 115, No. 3, 2008, pp. 493-511. [doi:10.1007/s00702-007-0859-5](https://doi.org/10.1007/s00702-007-0859-5)
- [4] H. M. Olbrich, G. Valerius, N. Rüsck, M. Buchert, T. Thiel, J. Hennig, D. Ebert and L. T. Van Elst, "Fronto-limbic Glutamate Alterations in First Episode Schizophrenia: Evidence from a Magnetic Resonance Spectroscopy Study," *World Journal of Biological Psychiatry*, Vol. 9, No. 1, 2008, pp. 59-63. [doi:10.1080/15622970701227811](https://doi.org/10.1080/15622970701227811)
- [5] G. W. Christison, M. F. Casanova, D. R. Weinberger, R. Rawlings and J. E. Kleinman, "A Quantitative Investigation of Hippocampal Pyramidal Cell Size, Shape, and Variability of Orientation in Schizophrenia," *Archives of General Psychiatry*, Vol. 46, No. 11, 1989, pp. 1027-1032. [doi:10.1001/archpsyc.1989.01810110069010](https://doi.org/10.1001/archpsyc.1989.01810110069010)
- [6] X. Duan, J. H. Chang, S. Ge, R. L. Faulkner, J. Y. Kim, Y. Kitabatake, X. B. Liu, C. H. Yang, J. D. Jordan, D. K. Ma, C. Y. Liu, S. Ganesan, H. J. Cheng, G. L. Ming, B. Lu, and H. Song, "Disrupted-in-Schizophrenia 1 Regulates Integration of Newly Generated Neurons in the Adult Brain," *Cell*, Vol. 130, No. 6, 2007, pp. 1146-1158. [doi:10.1016/j.cell.2007.07.010](https://doi.org/10.1016/j.cell.2007.07.010)
- [7] T. J. Raedler, M. B. Knable and D. R. Weinberger, "Schizophrenia as a Developmental Disorder of the Cerebral Cortex," *Current Opinion in Neurobiology*, Vol. 8, No. 1, 1998, pp. 157-161. [doi:10.1016/S0959-4388\(98\)80019-6](https://doi.org/10.1016/S0959-4388(98)80019-6)
- [8] T. H. McGlashan and R. E. Hoffman, "Schizophrenia as a Disorder of Developmentally Reduced Synaptic Connectivity," *Archives of General Psychiatry*, Vol. 57, No. 7, 2000, pp. 637-648. [doi:10.1001/archpsyc.57.7.637](https://doi.org/10.1001/archpsyc.57.7.637)
- [9] K. Ikemoto, A. Nishimura, T. Oda, I. Nagatsu and K. Nishi, "Number of Striatal D-Neurons Is Reduced in Autopsy Brains of Schizophrenics," *Legal Medicine*, Vol. 5, 2003, pp. S221-S224. [doi:10.1016/S1344-6223\(02\)00117-7](https://doi.org/10.1016/S1344-6223(02)00117-7)
- [10] C. B. Jaeger, G. Teitelman, T. H. Joh, V. R. Albert, D. H. Park and D. J. Reis, "Some Neurons of the Rat Central Nervous System Contain Aromatic-L-Amino-Acid Decarboxylase but Not Monoamines," *Science*, Vol. 219, No. 4589, 1983, pp. 1233-1235. [doi:10.1126/science.6131537](https://doi.org/10.1126/science.6131537)
- [11] A. A. Boulton, "Amines and Theories in Psychiatry," *Lancet*, Vol. 304, No. 7871, 1974, pp. 52-53.
- [12] A. A. Boulton and A. V. Juorio, "The Tyramines: Are They Involved in the Psychoses?" *Biological Psychiatry*, Vol. 14, No. 2, 1979, pp. 413-419.
- [13] K. Komori, T. Fujii, N. Karasawa, K. Yamada, M. Sakai and I. Nagatsu, "Some Neurons of the Mouse Cortex and Caudo-Putamen Contain Aromatic L-Amino Acid Decarboxylase but Monoamines," *Acta Histochemica et Cytochemica*, Vol. 24, No. 6, 1991, pp. 571-577. [doi:10.1267/ahc.24.571](https://doi.org/10.1267/ahc.24.571)
- [14] C. B. Jaeger, D. A. Ruggiero, V. R. Albert, T. H. Joh and D. J. Reis, "Immunocytochemical Localization of Aromatic-L-Amino Acid Decarboxylase," In: A. Björklund and T. Hökfelt, Eds., *Handbook of Chemical Neuroanatomy: Classical Transmitters in the CNS, Part I*. Elsevier, Amsterdam, 1984, pp. 387-408.
- [15] C. B. Jaeger, D. A. Ruggiero, V. R. Albert, D. H. Park, T. H. Joh and D. J. Reis, "Aromatic L-Amino Acid Decarboxylase in the Rat Brain: Immunocytochemical Localization in Neurons of the Rat Brain Stem," *Neuroscience*, Vol. 11, No. 3, 1984, pp. 691-713. [doi:10.1016/0306-4522\(84\)90053-8](https://doi.org/10.1016/0306-4522(84)90053-8)
- [16] Y. Tashiro, T. Kaneko, T. Sugimoto, I. Nagatsu, H. Kikuchi and N. Mizuno, "Striatal Neurons with Aromatic L-Amino Acid Decarboxylase-Like Immunoreactivity in the Rat," *Neuroscience Letters*, Vol. 100, No. 1-3, 1989, pp. 29-34. [doi:10.1016/0304-3940\(89\)90655-1](https://doi.org/10.1016/0304-3940(89)90655-1)
- [17] A. Mura, J. C. Linder, S. J. Young and P. M. Groves, "Striatal Cells Containing Aromatic L-Amino Acid Decarboxylase: An Immunohistochemical Comparison with Other Classes of Striatal Neurons," *Neuroscience*, Vol. 98, No. 3, 2000, pp. 501-511. [doi:10.1016/S0306-4522\(00\)00154-8](https://doi.org/10.1016/S0306-4522(00)00154-8)
- [18] K. Ikemoto, K. Kitahama, A. Jouvet, R. Arai, A. Nishimura, K. Nishi and I. Nagatsu, "Demonstration of L-Dopa Decarboxylating Neurons Specific to Human Striatum," *Neuroscience Letters*, Vol. 232, No. 2, 1997, pp. 111-114. [doi:10.1016/S0304-3940\(97\)00587-9](https://doi.org/10.1016/S0304-3940(97)00587-9)
- [19] K. Ikemoto, K. Kitahama, A. Jouvet, A. Nishimura, K. Nishi, T. Maeda and R. Arai, "A Dopamine-Synthesizing Cell Group Demonstrated in the Human Basal Forebrain by Dual Labeling Immunohistochemical Technique of Tyrosine Hydroxylase and Aromatic L-Amino Acid Decarboxylase," *Neuroscience Letters*, Vol. 243, No. 1-3, 1998, pp. 129-132. [doi:10.1016/S0304-3940\(98\)00103-7](https://doi.org/10.1016/S0304-3940(98)00103-7)
- [20] K. Kitahama, K. Ikemoto, A. Jouvet, I. Nagatsu, N. Sakamoto and J. Pearson, "Aromatic L-Amino Acid Decarboxylase and Tyrosine Hydroxylase Immunohistochemistry in the Adult Human Hypothalamus," *Journal of Chemical Neuroanatomy*, Vol. 16, 1998, pp. 43-55. [doi:10.1016/S0891-0618\(98\)00060-X](https://doi.org/10.1016/S0891-0618(98)00060-X)
- [21] K. Kitahama, K. Ikemoto, A. Jouvet, S. Araneda, I. Nagatsu, B. Raynaud, A. Nishimura, K. Nishi and S. Niwa, "Aromatic L-Amino Acid Decarboxylase-Immunoreac-

- tive Structures in Human Midbrain, Pons, and Medulla," *Journal of Chemical Neuroanatomy*, Vol. 38, No. 2, 2009, pp. 130-140. [doi:10.1016/j.jchemneu.2009.06.010](https://doi.org/10.1016/j.jchemneu.2009.06.010)
- [22] K. Ikemoto, "Significance of Human Striatal D-Neurons: Implications in Neuropsychiatric Functions," *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, Vol. 28, No. 3, 2004, pp. 429-434. [doi:10.1016/j.pnpbp.2003.11.017](https://doi.org/10.1016/j.pnpbp.2003.11.017)
- [23] J. R. Bunzow, M. S. Sonders, S. Arttamangkul, L. M. Harrison, G. Zhang, D. I. Quigley, T. Darland, K. L. Suchland, S. Pasumamula, J. L. Kennedy, S. B. Olson, R. E. Magenis, S. G. Amara and D. K. Grandy, "Amphetamine, 3,4-Methylenedioxyamphetamine, Lysergic Acid Diethylamide, and Metabolites of the Catecholamine Neurotransmitters Are Agonists of a Rat Trace Amine Receptor," *Molecular Pharmacology*, Vol. 60, No. 6, 2001, pp. 1181-1188.
- [24] B. Borowsky, N. Adham, K. A. Jones, R. Raddatz, R. Artymyshyn, K. L. Ogozalek, M. M. Durkin, P. P. Lakhani, J. A. Bonini, S. Pathirana, N. Boyle, X. Pu, E. Kouranova, H. Lichtblau, F. Y. Ochoa, T. A. Branchek and C. Gerald, "Trace Amines: Identification of a Family of Mammalian G Protein-Coupled Receptors," *Proceedings of the National Academy of Sciences of USA*, Vol. 98, No. 16, 2001, pp. 8966-8971. [doi:10.1073/pnas.151105198](https://doi.org/10.1073/pnas.151105198)
- [25] G. M. Miller, "The Emerging Role of Trace Amine-Associated Receptor 1 in the Functional Regulation of Monoamine Transporters and Dopaminergic Activity," *Journal of Neurochemistry*, Vol. 116, No. 2, 2011, pp. 164-176. [doi:10.1111/j.1471-4159.2010.07109.x](https://doi.org/10.1111/j.1471-4159.2010.07109.x)
- [26] Z. Xie and G. M. Miller, "Trace Amine-Associated Receptor 1 Is a Modulator of the Dopamine Transporter," *Journal of Pharmacology and Experimental Therapeutics*, Vol. 321, No. 1, 2007, pp. 128-136. [doi:10.1124/jpet.106.117382](https://doi.org/10.1124/jpet.106.117382)
- [27] Z. Xie and G. M. Miller, "Trace Amine-Associated Receptor 1 as a Monoaminergic Modulator in Brain," *Biochemical Pharmacology*, Vol. 78, No. 9, 2009, pp. 1095-1104. [doi:10.1016/j.bcp.2009.05.031](https://doi.org/10.1016/j.bcp.2009.05.031)
- [28] L. Lindemann, C. A. Meyer, K. Jeanneau, A. Bradaia, L. Ozmen, H. Bluethmann, B. Bettler, J. G. Wettstein, E. Borroni, J. L. Moreau and M. C. Hoener, "Trace Amine-Associated Receptor 1 Modulates Dopaminergic Activity," *Journal of Pharmacology and Experimental Therapeutics*, Vol. 324, No. 3, 2008, pp. 948-956. [doi:10.1124/jpet.107.132647](https://doi.org/10.1124/jpet.107.132647)
- [29] R. Zucchi, G. Chiellini, T. S. Scanlan and D. K. Grandy, "Trace Amine-Associated Receptors and Their Ligands," *British Journal of Pharmacology*, Vol. 149, No. 8, 2006, pp. 967-978. [doi:10.1038/sj.bjp.0706948](https://doi.org/10.1038/sj.bjp.0706948)
- [30] A. Bradaia, G. Trube, H. Stalder, R. D. Norcross, L. Ozmen, J. G. Wettstein, A. Pinard, D. Buchy, M. Gassmann, M. C. Hoener and B. Bettler, "The Selective Antagonist EPPTB Reveals TAAR1-Mediated Regulatory Mechanisms in Dopaminergic Neurons of the Mesolimbic System," *Proceedings of the National Academy of Sciences of USA*, Vol. 106, No. 47, 2009, pp. 20081-20086.
- [31] F. G. Revel, J. L. Moreau, R. R. Gainetdinov, A. Bradaia, T. D. Sotnikova, R. Mory, S. Durkin, K. G. Zbinden, R. Norcross, C. A. Meyer, V. Metzler, S. Chaboz, L. Ozmen, G. Trube, B. Pouzet, B. Bettler, M. G. Caron, J. G. Wettstein and M. C. Hoener, "TAAR1 Activation Modulates Monoaminergic Neurotransmission, Preventing Hyperdopaminergic and Hypoglutamatergic Activity," *Proceedings of the National Academy of Sciences of USA*, Vol. 108, No. 20, 2011, pp. 8485-8490. [doi:10.1073/pnas.1103029108](https://doi.org/10.1073/pnas.1103029108)
- [32] T. D. Wolinsky, C. J. Swanson, K. E. Smith, H. Zhong, B. Borowsky, P. Seeman, T. Branchek and C. P. Gerald, "The Trace Amine 1 Receptor Knockout Mouse: An Animal Model with Relevance to Schizophrenia," *Genes, Brain and Behavior*, Vol. 6, No. 7, 2007, pp. 628-639. [doi:10.1111/j.1601-183X.2006.00292.x](https://doi.org/10.1111/j.1601-183X.2006.00292.x)
- [33] K. Ikemoto, "Striatal D-Neurons: In New Viewpoints for Neuropsychiatric Research Using Post-Mortem Brains," *Fukushima Journal of Medical Science*, Vol. 54, No. 1, 2008, pp. 1-3.
- [34] A. Reif, S. Fritzen, M. Finger, A. Strobel, M. Lauer, A. Schmitt and K. P. Lesch, "Neural Stem Cell Proliferation Is Decreased in Schizophrenia, but Not in Depression," *Molecular Psychiatry*, Vol. 11, 2006, pp. 514-522. [doi:10.1038/sj.mp.4001791](https://doi.org/10.1038/sj.mp.4001791)
- [35] G. Degreef, M. Ashtari, B. Bogerts, R. M. Bilder, D. N. Jody, J. M. Alvir and J. A. Lieberman, "Volumes of Ventricular System Subdivisions Measured from Magnetic Resonance Images in First-Episode Schizophrenic Patients," *Archives of General Psychiatry*, Vol. 49, No. 7, 1992, pp. 531-537. [doi:10.1001/archpsyc.1992.01820070025004](https://doi.org/10.1001/archpsyc.1992.01820070025004)
- [36] G. Horga, J. Bernacer, N. Dusi, J. Entis, K. Chu, E. A. Hazlett, M. M. Haznedar, E. Kemether, W. Byne and M. S. Buchsbaum, "Correlations between Ventricular Enlargement and Gray and White Matter Volumes of Cortex, Thalamus, Striatum, and Internal Capsule in Schizophrenia," *European Archives of Psychiatry and Clinical Neuroscience*, Vol. 261, No. 7, 2011, pp. 467-476. [doi:10.1007/s00406-011-0202-x](https://doi.org/10.1007/s00406-011-0202-x)
- [37] T. E. Kippin, S. Kapur and D. van der Kooy, "Dopamine Specifically Inhibits Forebrain Neural Stem Cell Proliferation, Suggesting a Novel Effect of Antipsychotic Drugs," *Journal of Neuroscience*, Vol. 25, No. 24, 2005, pp. 5815-5023. [doi:10.1523/JNEUROSCI.1120-05.2005](https://doi.org/10.1523/JNEUROSCI.1120-05.2005)