

Dopamine Dilemma Overexcites the Hippocampus in Alzheimer's Disease

Dopamine neuron degeneration in the Ventral Tegmental Area causes hippocampal hyperexcitability in experimental Alzheimer's Disease

Spoleti E, La Barbera L, Cauzzi E, De Paolis ML, Saba L, Marino R, Sciamanna G, Di Lazzaro V, Keller F, Nobili A, Krashia P. *Mol Psychiatry*. 2024;29(5):1265–1280. doi:10.1038/s41380-024-02408-9.

Early and progressive dysfunctions of the dopaminergic system from the ventral tegmental area (VTA) have been described in Alzheimer's disease (AD). During the long pre-symptomatic phase, alterations in the function of parvalbumin interneurons (PV-INs) are also observed, resulting in cortical hyperexcitability represented by subclinical epilepsy and aberrant gamma oscillations. However, it is unknown whether the dopaminergic deficits contribute to brain hyperexcitability in AD. Here, using the Tg2576 mouse model of AD, we prove that reduced hippocampal dopaminergic innervation, due to VTA dopamine neuron degeneration, impairs PV-IN firing and gamma waves, weakens the inhibition of pyramidal neurons and induces hippocampal hyperexcitability via lower D2 receptor-mediated activation of the cAMP-response element binding protein (CREB) pathway. These alterations coincide with reduced PV-IN numbers and perineuronal net density. Importantly, L-DOPA and the selective D2 receptor agonist quinpirole rescue p-CREB levels and improve the PV-IN-mediated inhibition, thus reducing hyperexcitability. Moreover, similarly to quinpirole, sumanirole—another D2 receptor agonist and a known anticonvulsant—not only increases p-CREB levels in PV-INs but also restores gamma oscillations in Tg2576 mice. Conversely, blocking the dopaminergic transmission with sulpiride (a D2-like receptor antagonist) in wild-type mice reduces p-CREB levels in PV-INs, mimicking what occurs in Tg2576. Overall, these findings support the hypothesis that the VTA dopaminergic system integrity plays a key role in hippocampal PV-IN function and survival, disclosing a relevant contribution of the reduced dopaminergic tone to aberrant gamma waves, hippocampal hyperexcitability, and epileptiform activity in early AD.

Commentary

Alzheimer's disease (AD) is a progressive neurodegenerative disease, and it is the primary cause of cognitive impairment and dementia in the aging population. In addition to cognitive dysfunction, AD is characterized by neuropathological hallmarks that include amyloid- β (A β) peptides, plaques, neurofibrillary tangles, and neuroinflammation. Current therapeutics for AD include acetylcholinesterase inhibitors that attempt to treat cognitive deficits. Thus, there is a critical need to identify treatments that target the underlying mechanisms for AD symptoms in order to prevent or slow disease progression.

Compared to the general population, there is a significantly higher incidence of epilepsy in patients with AD, and over 40% of AD patients without a history of epilepsy exhibit subclinical epileptiform activity.¹ Mouse models of AD also demonstrate epileptiform activity and increased seizure susceptibility prior to the onset of behavioral abnormalities and AD neuropathology. Together, these observations suggest a shared mechanism

between epilepsy and AD and that this commonality could be leveraged for treatment development in AD.

Gamma wave oscillations are generated by the synchronous activity of fast-spiking parvalbumin (PV) interneurons, and these oscillations are important for higher-order processing such as cognitive function. In AD, there is evidence of PV interneuron dysfunction which subsequently leads to aberrant gamma oscillations and network hyperexcitability. Moreover, restoration of PV interneuron function has been shown to rescue aberrant gamma oscillations in AD, which in turn, reduces A β deposition and ameliorates learning and memory deficits.^{2,3} While the mechanism underlying PV interneuron dysfunction in AD remains to be elucidated, it is hypothesized that deficits in dopaminergic signaling to PV interneurons might contribute to alterations in gamma oscillations.

In the current study, Spoleti and colleagues tested the hypothesis that disruption of the dopaminergic system leads to altered PV interneuron function and neuronal





hyperexcitability in AD.⁴ The authors used the Tg2576 mouse model of AD, which harbors the Swedish mutation (KM670/671NL) that causes overexpression of a mutant form of amyloid precursor protein (APP). Tg2576 mutants have increased levels of A β , amyloid plaque deposition, and progressive deficits in synaptic plasticity and cognitive behavior. Spoleti et al.⁴ observed reduced levels of tyrosine hydroxylase (TH), an enzyme needed for the synthesis of dopamine, and TH⁺ fiber density in the dorsal hippocampus of 3- and 7-month-old Tg2576 mice. These observations are consistent with the authors' previous work where they detected degeneration of dopaminergic neurons in the VTA and lower levels of hippocampal dopamine in Tg2576 mutants by 2–3 months of age.⁵ The authors also found fewer dopaminergic contacts onto hippocampal PV interneurons and fewer TH⁺ neurons in the VTA of Tg2576 mice. Since dopaminergic signaling is involved in CREB phosphorylation, the authors also investigated whether CREB markers were affected. Notably, compared to wild-type (WT) mice, lower levels of p-CREB and c-Fos, a marker of neuronal activity, were observed in PV interneurons of 3-month-old Tg2576 mice, while levels were not different in 1-month-old Tg2576 mice. The authors also examined hippocampal excitability in the Tg2576 mutants. Decreased power of gamma oscillations, reduced evoked excitability of the PV interneurons, and fewer PV interneurons were observed in the CA1 region of the hippocampus of 7-month-old Tg2576 mutants. In addition, Spoleti et al., noted reduced spontaneous inhibitory postsynaptic currents (sIPSCs) in 3-month-old Tg2576 mutants and an even greater reduction in sIPSCs in 7-month-old mutants.⁴ This age-related progressive decrease in inhibitory drive onto the PV interneurons correlated with an increase in excitability of the hippocampus in the Tg2576 mutants. Altogether, the current study is the first to identify age-related alterations in the dopaminergic system that directly reduce PV interneuron function in the Tg2576 mouse model of AD,⁴ which suggests that reduced dopaminergic function might contribute to the observed neuronal hyperexcitability in AD.

Previous studies have shown that dopamine can regulate the function of PV interneurons through the D2 receptors.^{6,7} As such, Spoleti et al., speculated that their observation of reduced levels of p-CREB and c-Fos in PV interneurons of Tg2576 mutants might be a result of reduced activation of the D2 receptors. Consistent with their hypothesis, the authors found that application of the D2 receptor agonist quinpirole to hippocampal slices increased levels of p-CREB and c-Fos in PV interneurons from 3-month-old Tg2576 mice compared to vehicle-treated WT mice. Similarly, intraperitoneal administration of the D2 receptor agonist sumanirole to Tg2576 mice also increased levels of p-CREB and the overall power of gamma oscillations. In contrast, the application of the D2 receptor antagonist sulpiride onto WT hippocampal slices reduced p-CREB and c-Fos in PV interneurons to levels observed in Tg2576 mice. Finally, increasing dopamine levels via sub-chronic L-DOPA administration (4 consecutive days) reduced hippocampal excitability in the Tg2576 mice. Importantly, Spoleti and colleagues demonstrated that activation of D2

receptors restored PV interneuron function and normalized neuronal excitability in the Tg2576 mice,⁴ which might provide a novel therapeutic avenue for AD.

Several APP overexpressing mouse lines exhibit aberrant gamma oscillations.⁸ Given the findings in the current study, it is possible that reduced dopamine innervation and PV interneuron dysfunction might be underlying mechanisms for neuronal hyperexcitability in multiple mouse models of early-onset AD. To increase translational relevance, it would be worthwhile to establish whether reduced dopamine innervation and neuronal hyperexcitability are also observed in late-onset or tau AD models. Furthermore, while Spoleti et al., observed reduced dopaminergic input onto PV interneurons in the Tg2576 mutants,⁴ it would also be valuable to explore whether other interneuron subtypes are affected. Spoleti et al., established the contribution of the D2 receptor to PV interneuron function and hippocampal excitability in AD,⁴ which provides a potential novel therapeutic target for preventing or slowing disease progression in AD. Further research is warranted to determine the extent to which D2 receptor activation can ameliorate other clinically relevant features of AD, including cognitive dysfunction and AD neuropathology.

While not the focus of the current study, the findings from this study might also have important implications in the treatment of epilepsy. As previous studies have demonstrated the anti-convulsive effects of D2 receptor agonists,⁹ it is not surprising that sumanirole and quinpirole restored more normal levels of neuronal excitability in the Tg2576 mice. Furthermore, a recent study showed that administration of the D2 receptor agonist sumanirole led to prolonged activation of PV interneurons.⁷ Thus, the findings from Spoleti and colleagues⁴ provide a potential mechanism for the anti-convulsive effects of D2 receptor activation. Together, these observations raise the possibility that D2 receptor agonists could provide a viable treatment for epilepsy subtypes that are characterized by PV interneuron dysfunction. For example, impaired PV interneuron synaptic transmission has been observed in a mouse model of Dravet syndrome,¹⁰ and interestingly, current treatment approaches include strategies aimed at increasing the excitability of GABAergic interneurons.¹¹ Further research into the clinical use of D2 receptor agonists for the treatment of epilepsy is therefore warranted.

Jennifer C. Wong 

Department of Human Genetics,
Emory University

ORCID iD

Jennifer C. Wong  <https://orcid.org/0000-0003-0602-6351>

Declaration of Conflicting Interests

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.



Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Vossel KA, Ranasinghe KG, Beagle AJ, et al. Incidence and impact of subclinical epileptiform activity in Alzheimer's disease. *Ann Neurol*. 2016;80(6):858-870.
2. Etter G, van der Veldt S, Manseau F, Zarrinkoub I, Trillaud-Doppia E, Williams S. Optogenetic gamma stimulation rescues memory impairments in an Alzheimer's disease mouse model. *Nat Commun*. 2019;10(1):5322.
3. Kastanenko KV, Hou SS, Shakerdige N, et al. Optogenetic restoration of disrupted slow oscillations halts amyloid deposition and restores calcium homeostasis in an animal model of Alzheimer's disease. *PLoS One*. 2017;12(1):e0170275.
4. Spoletti E, La Barbera L, Cauzzi E, et al. Dopamine neuron degeneration in the Ventral Tegmental Area causes hippocampal hyperexcitability in experimental Alzheimer's Disease. *Mol Psychiatry*. 2024;29(5):1265-1280.
5. Nobili A, Latagliata EC, Viscomi MT, et al. Dopamine neuronal loss contributes to memory and reward dysfunction in a model of Alzheimer's disease. *Nat Commun*. 2017;8:14727.
6. Tomasella E, Bechelli L, Ogando MB, et al. Deletion of dopamine D(2) receptors from parvalbumin interneurons in mouse causes schizophrenia-like phenotypes. *Proc Natl Acad Sci USA*. 2018;115(13):3476-3481.
7. Brodovskaya A, Kapur J. Anticonvulsant dopamine type 2 receptor agonist activates inhibitory parvalbumin interneurons. *Epilepsia*. 2021;62(9):e147-e152.
8. Palop JJ, Mucke L. Network abnormalities and interneuron dysfunction in Alzheimer disease. *Nat Rev Neurosci*. 2016;17(12):777-792.
9. Weinshenker D, Szot P. The role of catecholamines in seizure susceptibility: new results using genetically engineered mice. *Pharmacol Ther*. 2002;94(3):213-233.
10. Kaneko K, Currin CB, Goff KM, et al. Developmentally regulated impairment of parvalbumin interneuron synaptic transmission in an experimental model of Dravet syndrome. *Cell Rep*. 2022;38(13):110580.
11. Tanenhaus A, Stowe T, Young A, et al. Cell-selective adeno-associated virus-mediated SCN1A gene regulation therapy rescues mortality and seizure phenotypes in a Dravet syndrome mouse model and is well tolerated in nonhuman primates. *Hum Gene Ther*. 2022;33(11-12):579-597.