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Letter to Editors

Expanding on possible mechanisms for tardive dyskinesia: A response to Ali, Roque, and Mallakh

The most popular theory explaining tardive dyskinesia (TD) is as a result of D2 receptor (D2R) hypersensitivity compensating for the blockade of D2Rs by antipsychotics [1]. The paper by Ali, Roque, and Mallakh contests this theory on the grounds that there is a lack of studies demonstrating D2R supersensitivity in humans treated with antipsychotics and the slight increase in D2 receptor density measured by PET study would be insufficient to account for movement disorder, and furthermore that this hypothesis fails to explain the persistence of TD long after antipsychotic discontinuation [2].

Their proposed theory, in contrast, states that TD has a largely presynaptic etiology in which blockade of postsynaptic dopamine receptors causes excess dopamine reuptake back into the terminal, increasing presynaptic vesicular concentrations and the quanta subsequently released by the presynaptic neuron. It supplements this theory by citing a study of mentally disabled patients showing increased tardive dyskinesia in phenylketonuria (PKU) patients [3], who have higher blood, plasma, and brain levels of phenylalanine, a dopamine precursor.

However, the major biosynthetic pathway through which phenylalanine is converted to dopamine includes its conversion to tyrosine by phenylalanine hydroxylase [4], the enzyme that is deficient in PKU patients [5], and therefore increased phenylalanine levels in these patients may not correlate with increased dopamine levels.

D2Rs are the type found on indirect pathway medium spiny neurons within the striatum, that project to the globus pallidus interna via the globus pallidus externa, a pathway responsible for the inhibition of unwanted movements [6]. Hypersensitivity of this pathway would not intuitively lead to unwanted movements. I propose that D1 receptor (D1R) hypersensitivity underlies TD - D1R-containing GABAergic neurons are direct pathway medium spiny neurons, which project directly to the globus pallidus interna and are involved in the generation of movements [6]. Hypersensitivity of this pathway would explain excess movements and was implicated in Parkinsonian dyskinesia via extracellular signal-regulated kinase (ERK) phosphorylation of D1Rs [7]. Increased ERK phosphorylation has been observed in the striata of mice after antipsychotic treatment [8]. Most striatal neurons are D1-type or D2-type MSNs [9] and the increase in D2 neurons was deemed insufficient to account for the increased protein levels observed in western blot [10]. While other factors could explain this discrepancy, it does elucidate a potential molecular pathway for my proposed mechanism. Additionally, behavioral supersensitivity was also linked to treatment with D1R antagonists in the rat model [11].

This hypothesis has been overlooked in the past because the majority of antipsychotics were thought to target D2Rs. However, many antipsychotics also have affinity for D1Rs [12–15] and activate D1-receptors in animal models [16]. Polymorphisms affecting the D1 receptor were shown to be significant in influencing susceptibility to TD in schizophrenic patients [17] and animal models [18], confriming a potential role for this receptor.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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