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Modulation of intracellular dopamine signaling by aripiprazole may cause malocclusion as an extrapyramidal symptom

Aripiprazole, a dopamine partial agonist, is one of the most widely prescribed atypical antipsychotics and its use in children and adolescents has become common. However, due to its favorable side effect profile, its potential for inducing extrapyramidal symptoms (EPS) in children and adolescents has been neglected. Recently, we reported an adolescent female suffering from aripiprazole-induced EPS called open bite. Open bite is a type of malocclusion in which the upper and lower teeth do not touch when the mouth is completely closed, leaving a gap between the upper and lower teeth (Fig. 1). If open bite is not treated, it can result in speech disorders such as lisp, increased wear of the back teeth, and physical complaints such as stiff shoulders and headaches. In the patient we reported, aripiprazole was discontinued and the open bite resolved.

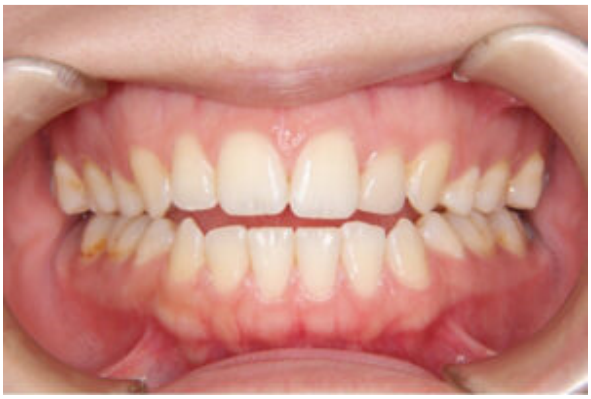

Fig. 1. Open bite. When the mouth is completely closed, the upper and lower teeth do not touch.

Coustals et al. warn that while aripiprazole is effective for psychiatric disorders in children and adolescents, EPS appears along with weight gain and drowsiness (*J Child Adolesc Psychopharmacol* 2021;31(1):4-32.) Bernagie et al. found a 17.1% incidence of EPS in a meta-analysis of aripiprazole treatment in children and adolescents, significantly higher than placebo (*CNS Drugs* 2016;30(9):807-18). Varela et al. found that aripiprazole treatment increased D2 receptor expression and sustained amphetamine-induced behavioral changes in juvenile rats, indicating that aripiprazole may act as a potent D2-blocker in the immature brain stage (*J Psychopharmacol* 2014;28(4):376-86). Dopamine partial agonists, as well as complete blockers, should also be noted in EPS.

The exact mechanism by which partial agonists cause EPS is not known, but we believe that aripiprazole reduces intracellular dopamine signaling at the molecular level. When the receptor and ligand interact, the receptor conformation is changed. When an antagonist is attached to the receptor, it assumes an antagonist conformation and intracellular signaling does not occur. On the other hand, when an agonist is attached, the receptor assumes an agonist conformation and intracellular signal transduction begins. The most important difference between complete blockers and partial agonists is that partial agonists initiate intracellular signaling. Dopamine D2 receptors are one of the G protein-coupled receptors (GPCRs). Binding of a full agonist to the dopamine D2 receptor results in a conformational change in the α-subunit (Gα), releasing GDP

and instead binding GTP, which becomes the active form and transmits dopamine signaling. Partial agonists result in weaker signaling, with Gα dissociation being lower than that of dopamine. At the same time, the GPCR is phosphorylated and β-arrestin attaches, generating β-arrestin signaling. The GPCR is then coated with clathrin, moves into the cytoplasm, and internalizes, resulting in desensitization. Desensitization is a phenomenon in which intracellular signaling by agonists is attenuated from the initial response. Attachment of dopamine partial agonists to GPCRs may weaken dopamine signaling in the G protein pathway and desensitize GPCRs in the β-arrestin pathway, resulting in decreased intracellular dopamine signaling (Fig. 2).

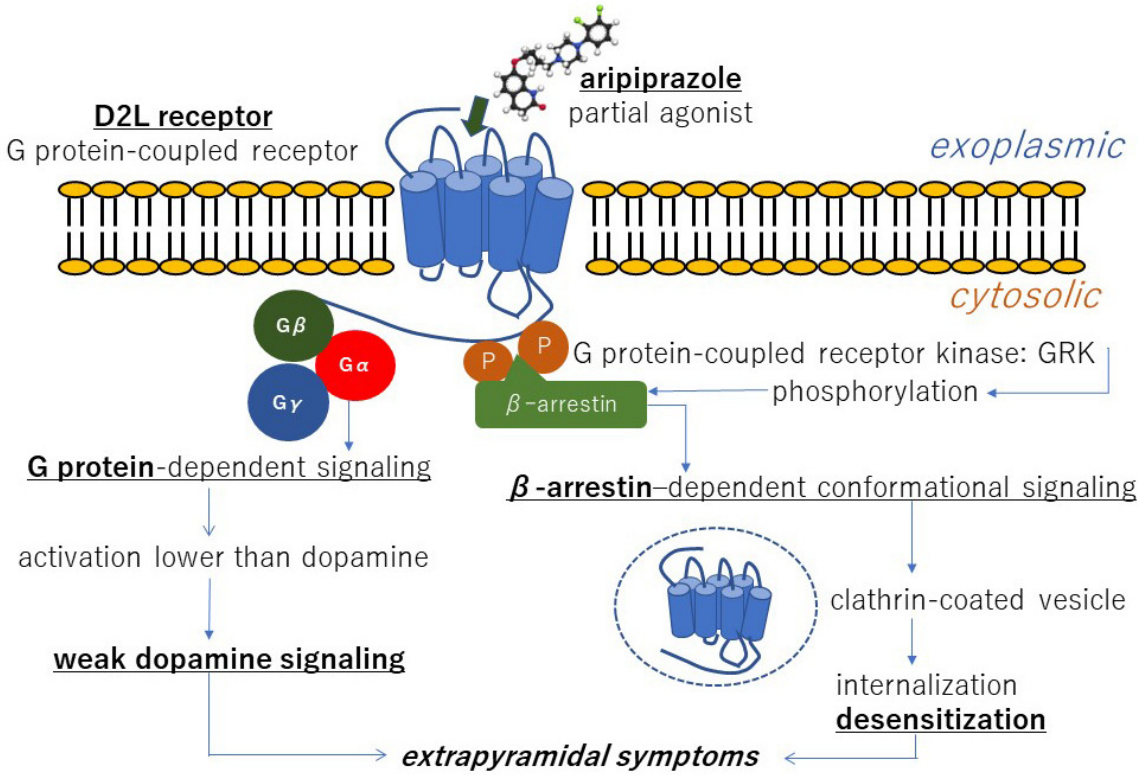

Fig. 2. Mechanism by which dopamine partial agonists cause EPS. Both the G-protein pathway and the β-arrestin pathway can decrease dopamine signaling due to conformational changes.

Open bite implies that aripiprazole can induce EPS unexpectedly in adolescents. We speculate that there may be differences in the development of these systems in adults and children, and that EPS is more likely to occur in children and adolescents. When aripiprazole is administered to children and adolescents, especially for the first time, the emergence of any type of EPS should be carefully monitored. Future research is needed to determine how partial agonists alter dopamine signaling in the cortico-basal ganglia loop in children and adolescents to prevent EPS in the oral-facial region.

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