Molecular Psychiatry
https://doi.org/10.1038/s41380-018-0022-8

CORRESPONDENCE

Exercise-induced hippocampal neurogenesis: 5-HT_3 receptor antagonism by antipsychotics as a potential limiting factor in Schizophrenia

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Received: 13 October 2017 / Revised: 19 December 2017 / Accepted: 15 January 2018

Aerobic exercise is a well-understood stimulus to hippocampal plasticity [1]. Exercise for individuals with Schizophrenia is especially promising as smaller hippocampal volume (HV) is a core feature, and volume increases are associated with improved clinical and cognitive outcomes [2]. One major component of hippocampal plasticity is adult neurogenesis. Evidence has demonstrated significant deficits in hippocampal cell proliferation or neurogenesis in post-mortem brain tissue of patients with Schizophrenia [3], suggesting that restoration of hippocampal neurogenesis (e.g., by exercise) may have therapeutic implications.

Over the past decade, several studies have investigated the effects of exercise on brain structures, including HV, in individuals with Schizophrenia. However, results have not been consistent. Pajonk and colleagues (2010) demonstrated that following 3-month aerobic training, relative HV significantly increased by 12 and 16% in patients and healthy participants, respectively, but not in patients who played table football (−1%) [1]. The study design was replicated with larger samples using the identical protocol; however, significant increases in HV were not observed in patients or healthy participants [4]. This is in line with another study that utilized 6 months of combined aerobic and resistance training [5]. Conflicting results as to the effects of aerobic exercise on HV are also present among individuals in the early stages of illness [6, 7].

Therefore, factors that are responsible for such inconsistent results need to be identified. Although variations in exercise protocols and image analysis strategies between the existing studies may be responsible, the recent study by Kondo and colleagues (2015) led us to consider 5-HT_3 receptor antagonism by antipsychotics as a potential key factor that impedes exercise-induced HV expansion in individuals with Schizophrenia [8]. The study demonstrated that the 5-HT_3 receptor, a ligand-gated ion channel, is required for exercise-induced hippocampal neurogenesis and antidepressant effects, as shown using a 5-HT_{3A} receptor subunit-deficient (*htr3a*$^{-/-}$) mouse model [8]. In this study, with no difference at baseline, hippocampal cell proliferation and neurogenesis were enhanced by exercise in the wild-type, but not in the *htr3a*$^{-/-}$ mice [8]. Furthermore, stimulation of 5-HT_3 receptors using a selective 5-HT_3 receptor agonist promoted neurogenesis in the wild-type, but not in the *htr3a*$^{-/-}$ mice [8].

Given this evidence that 5-HT_3 receptors are essential for exercise-induced hippocampal neurogenesis, the fact that some antipsychotics antagonize 5-HT_3 receptors deserves attention. To this point, the National Institute of Mental Health Psychoactive Drug Screening Program (NIMH PDSP) demonstrated via radioligand binding assays that antipsychotics, such as aripiprazole ($K_i = 628$ nM), clozapine ($K_i = 241$ nM), loxapine ($K_i = 190$ nM), and olanzapine ($K_i = 202$ nM), have moderate affinities for 5-HT_3 (cloned human) receptors. Rammes and colleagues (2004) demonstrated, using the patch clamp technique, that apart from risperidone, various antipsychotics at therapeutic concentrations (i.e., clozapine, flupentixol, fluphenazine, haloperidol, levomepromazine, and thioridazine) antagonized 5-HT-evoked Na^+-inward and Ca^{2+}-inward currents through 5-HT_3 receptors stably expressed in human embryonic kidney 293 cells in a competitive (for clozapine) and noncompetitive (for all the other antipsychotics) manner [9]. Aside from their inhibitory effects on Na^+ currents, most of these antipsychotics showed a higher potency against 5-HT_{3A} receptor-mediated Ca^{2+} currents (e.g., IC_{50}

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Published online: 08 February 2018

= 120 nM for flupentixol, 140 nM for haloperidol, and 610 nM for thioridazine) [9]. Therefore, data suggest that various first-generation and second-generation antipsychotics have antagonistic properties for 5-HT_3 receptors, and we hypothesize that this may be a key factor responsible for the inconsistent exercise-induced HV expansion observed in Schizophrenia patients treated with antipsychotics [1, 4–7].

Taken together, we highlight and extend the findings of Kondo and colleagues (2015) to make a suggestion that the difficulty experienced by recent exercise trials to promote hippocampal plasticity in individuals with Schizophrenia may be attributed to 5-HT_3 receptor antagonism by antipsychotics. We acknowledge that for both patients and healthy persons, the failure to observe a volume change may be due to insensitivity of the image analysis strategies [4, 5]. However, there also may be different mechanisms of HV change in patients and healthy persons when it does occur, and likewise, different mechanisms when it is not observed. For instance, Pajonk and colleagues (2010) showed that there was a change in metabolism in the hippocampus following exercise in patients but not in the healthy persons, yet both had a volume change [1]. Thus, the mechanism of HV change may be different, and likewise, the factors obscuring or blocking a volume change may be different in patients and healthy persons. Just because healthy participants are not exposed to 5-HT_3 antagonism, it does not mean that this mechanism is irrelevant in the patient group.

Future studies should compare the effects of different antipsychotics on exercise-induced hippocampal neurogenesis in animal models or on exercise-induced hippocampal plasticity in individuals with Schizophrenia. For instance, it can be speculated that larger increases in HV would be observed in those treated with antipsychotics having no affinity for 5-HT_3 receptors (e.g., risperidone) than antipsychotics that antagonize 5-HT_3 receptors (e.g., clozapine) [9]. It would also be of interest to investigate the effects of adding 5-HT_3 antagonists or agonists to antipsychotic treatment on exercise-induced hippocampal neurogenesis or plasticity. While 5-HT_3 antagonists, such as ondansetron, have been investigated for their add-on effects on the symptoms of Schizophrenia (e.g., NCT01121042), their effects should also be examined during exercise to see whether hippocampal neurogenesis or plasticity may be impaired as a result of 5-HT_3 antagonism. Furthermore, evidence suggests that varenicline, a widely used smoking cessation agent, is a potent agonist of human 5-HT_3 receptors and binds to these receptors at clinically relevant concentrations [10]. Thus, whether varenicline treatment would enhance exercise-induced hippocampal plasticity warrants future investigation.

Compliance with ethical standards

Conflict of interest AMB has received grants from Bristol-Myers Squibb and the Canadian Institutes of Health Research. WGH has received consulting fees from MDH Consulting, In Silico (no honorarium), Novartis, Eli Lilly, Roche, Otsuka, and Lundbeck; and received grants from the Canadian Institutes of Health Research. RMP has received consulting fees from Janssen, Lundbeck, and Otsuka; is on the speaker's bureau for Janssen, Lundbeck, and Otsuka; and has received grants from the Canadian Institutes of Health Research. DDK declares that he has no conflict of interest.

References

1. Pajonk FG, Wobrock T, Gruber O, Scherk H, Berner D, Kaizl I, et al. Hippocampal plasticity in response to exercise in schizophrenia. Arch Gen Psychiatry. 2010;67:133–43.
2. Lappin JM, Morgan C, Chalavi S, Morgan KD, Reinders AA, Fearon P, et al. Bilateral hippocampal increase following first-episode psychosis is associated with good clinical, functional and cognitive outcomes. Psychol Med. 2014;44:1279–91.
3. Allen KM, Fung SJ, Weickert CS. Cell proliferation is reduced in the hippocampus in schizophrenia. Aust N Z J Psychiatry. 2016;50:473–80.
4. Malchow B, Keeser D, Keller K, Hasan A, Rauchmann BS, Kimura H, et al. Effects of endurance training on brain structures in chronic schizophrenia patients and healthy controls. Schizophr Res. 2016;173:182–91.
5. Scheewe TW, van Haren NE, Sarkisyan G, Schnack HG, Brouwer RM, de Glint M, et al. Exercise therapy, cardiorespiratory fitness and their effect on brain volumes: a randomised controlled trial in patients with schizophrenia and healthy controls. Eur Neuropsychopharmacol. 2013;23:675–85.
6. Rosenbaum S, Lagopoulos J, Curtis J, Taylor L, Watkins A, Barry BK, et al. Aerobic exercise intervention in young people with schizophrenia spectrum disorders; improved fitness with no change in hippocampal volume. Psychiatry Res. 2015;232:200–1.
7. Lin J, Chan SKW, Lee EHM, Chang WC, Tse M, Su WW, et al. Aerobic exercise and yoga improve neurocognitive function in women with early psychosis. NPJ Schizophr. 2015;1:15047.
8. Kondo M, Nakamura Y, Ishida Y, Shimada S. The 5-HT3 receptor is essential for exercise-induced hippocampal neurogenesis and antidepressant effects. Mol Psychiatry. 2015;20:1428–37.
9. Rammes G, Eisensamer B, Ferrari U, Shapa M, Gimpl G, Gilling K, et al. Antipsychotic drugs antagonize human serotonin type 3 receptor currents in a noncompetitive manner. Mol Psychiatry. 2004;9:846–58.
10. Lummis SC, Thompson AJ, Bencherif M, Lester HA. Varenicline is a potent agonist of the human 5-hydroxytryptamine3 receptor. J Pharmacol Exp Ther. 2011;339:125–31.