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Bell-shaped dose-response curve of antipsychotic drugs and dopaminergic auto-receptors: a hypothesis

Kentaro Kohno, Takeshi Terao, Hirofumi Hirakawa, Nobuyoshi Ishii

Department of Neuropsychiatry, Oita University Faculty of Medicine, Japan

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To the Editor: As for a dose-response relationship of antidepressant doses and the efficacy, interestingly, some antidepressants showed a bell-shaped dose-response curve where increasing doses leads to increasing efficacy and further increasing doses leads to decreasing efficacy. In fact, a meta-analysis [1] showed that SSRIs consisting of citalopram, escitalopram, fluoxetine, paroxetine and sertraline, and mirtazapine had a bell-shaped dose-response curve. Here, the first part of the curve shows increasing efficacy which may reflect the simple dose-response relationship of antidepressants whereas the second part could have not been explained, yet. Very recently, we proposed a hypothesis that the negative feedback by 5-HT_{1A} auto-receptors may decrease the efficacy of SSRIs and make the second part of the bell-shaped dose-response curve [2].

Also in antipsychotic drugs, there exist similar bell-shaped dose-response curves. A dose-response meta-analysis [3] identified the near-maximal effective doses (85-95% effective doses: ED85 to ED95) of 20 antipsychotics, showing that the upper limits of licensed doses were higher than the maximum effective doses in some drugs with bell-shaped dose-response curves [3]. For example, the maximum licensed doses of aripiprazole (30 mg/day) and risperidone (16 mg/day) far exceeded the ED95 s for these drugs (11.5 mg/day and 6.3 mg/day, respectively) [3]. The authors provided a likely reason for the bell-shaped curve that although efficacy plateaus beyond a certain dose, the frequency of extrapyramidal side effects continues to increase, and that these extrapyramidal side effects may mimic negative symptoms, which may contribute to higher rating scores.

We would like to propose another reason for the bell-shaped dose-response curve of some antipsychotic drugs as our hypothesis. Auto-receptors on dopamine neurons are comprised of the D_2-subtype of dopamine receptors, which are located on the soma and dendrites of midbrain dopamine neurons in the ventral tegmental area and substantia nigra pars compacta, as well as on their axon terminals in projection areas [4]. As feedback regulators, auto-receptors directly modulate dopamine-dependent transmission activity through the activation of potassium conductance, and indirectly modulate this activity through downstream control of the expression of tyrosine hydroxylase and the plasma membrane dopamine transporter [4]. Activation of these auto-receptors decreases both the excitability of dopamine neurons and the release of dopamine [4]. In fact, positron emission tomography studies with [^{11}C]raclopride and L-[β-^{11}C]DOPA demonstrated the involvement of dopaminergic D_2 auto-receptors on presynaptic dopamine synthesis capacity in healthy men taking risperidone [5] and aripiprazole [6]. These observations produce another potential explanation for the bell-shaped curve as shown in Figure 1. Specifically, beyond a certain dose, there is a negative feedback mechanism via dopaminergic D_2 auto-receptors. Here, excessive antagonism to the dopamine D_2 auto-receptors strongly increases dopamine synthesis and secretion. This may, in turn, overcome dopamine D_2 postsynaptic

Corresponding author: Takeshi Terao, MD, PhD, Professor, Department of Neuropsychiatry, Oita University Faculty of Medicine, Idaigaoka 1-1, Hasama-machi, Yufu, Oita 879-5593, Japan; E-mail: terao@oita-u.ac.jp

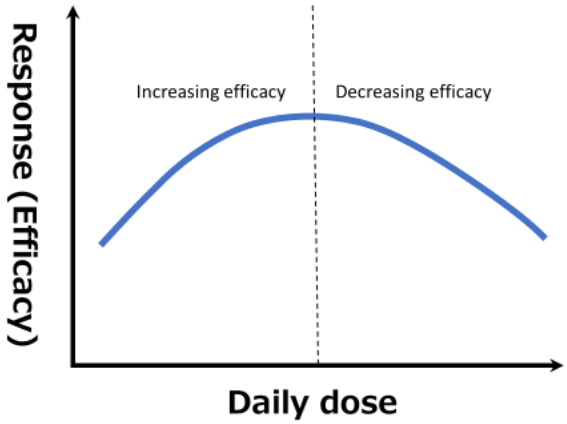

Figure 1.
A bell-shaped dose-response curve of some antipsychotic drugs
The left half of the curve showing increasing efficacy which may reflect the simple dose-response relationship of antipsychotic drugs while the right half could have not been explained, yet. Our hypothesis is that a negative feedback mechanism via dopaminergic auto-receptors may constitute the right half of the bell-shaped dose-response curve. More clearly, the efficacy of antipsychotic drugs may decrease in response to dose increase beyond a certain point where the effects of negative feed-back by dopaminergic auto-receptors surpass the effects of post-synaptic dopamine D_2 postsynaptic antagonism.

antagonism and exacerbate psychotic symptoms.

Limitations of this hypothesis are that several but not all antipsychotic drugs show bell-shaped dose-response curves although it is possible that higher than usual doses can make bell-shaped curves in most antipsychotic drugs, that it is unknown whether the first or the second generation antipsychotic drugs are prone to show bell-shaped dose-response curves, and that to our knowledge there are no research papers or case reports showing that the reduction of antipsychotic doses brought about the improvement of their psychotic symptoms although according to our clinical experiences there exist such patients who responded better to lower antipsychotic doses than to higher doses.

CONFLICT OF INTEREST

None

REFERENCES

[1] Furukawa TA, Cipriani A, Cowen PJ, Leucht S, Egger M, Salanti G. Optimal dose of selective serotonin reuptake inhibitors, venlafaxine, and mirtazapine in major depression: a systematic review and dose-response meta-analysis. Lancet Psychiatry 2019; 6(7): 601-609.

[2] Terao T, Ishii N, Hirakawa H, Aoshima E. Is the bell-shaped dose-response curve of the selective serotonin reuptake inhibitor due to 5-HT_{1A} auto-receptors? [published online ahead of print, 2020 Mar 16]. Med Hypotheses 2020; 140: 109681. doi: 10.1016/j.mehy.2020.109681

[3] Leucht S, Crippa A, Siafis S, Patel MX, Orsini N, Davis JM. Dose-Response Meta-Analysis of Antipsychotic Drugs for Acute Schizophrenia Am J Psychiatry 2020; 177(4): 342-353.

[4] Ford CP: The role of D2-auto-receptors in regulating dopamine neuron activity and transmission. Neuroscience 2014; 282: 13-22.

[5] Ito H, Takano H, Arakawa R, et al: Effects of dopamine D2 receptor partial agonist antipsychotic aripiprazole on dopamine synthesis in human brain measured by PET with L-[β-11C] DOPA. PLoS One 2012; 7: e46488.

[6] Ito H, Takano H, Takahashi H, et al: Effects of the antipsychotic risperidone on dopamine synthesis in human brain measured by positron emission tomography with L-[beta-11C]DOPA: a stabilizing effect for dopaminergic neurotransmission? J Neurosci 2009; 29: 13730-13734.