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CORRESPONDENCE

$GABA_B$ receptor, clozapine, and catatonia—a complex triad

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To the Editor:

We were very pleased to read the article by Nair et al. [1], who rightly highlighted the pharmacological uniqueness of clozapine and hypothesized its action as a modulator of the gamma-aminobutyric acid B receptor ($GABA_B$). Such mechanisms may not only be relevant for treatment-resistant schizophrenia (SZ), but also for catatonia. We suggest that besides positive symptoms (e.g., delusions, hallucinations, and first-rank symptoms), catatonia can also be considered as one of the paradigmatic examples of aberrant fluctuation of $GABA_{A+B}$ activity [2]. Here, we will refer to three main reasons in support of our claim:

First, catatonia is a psychomotor syndrome (occurring in 9–17% of acute mental disorders) characterized by motor, affective, and behavioral anomalies [3–5]. Affective symptoms on the perceptual-experiential level such as anxiety (fear), aggression, flat affect, negative affect, and affect incontinence are intrinsic to catatonia, but can also occur in a variety of mental disorders such as SZ, bipolar disorder (BD), and major depressive disorder (MDD). We agree with Nair et al. that SZ patients, whether catatonic or not, might misinterpret environmental stimuli [1]. Furthermore, the inability to control emotions and affects has a strong impact on behavioral and motor functions [6]. For this reason, in DSM-5, catatonia can be used as a specifier to characterize an underlying mental disorder in more clinical detail. In ICD-11, catatonia will be recognized as an independent diagnostic entity [7]. Despite these developments, patients with typical catatonic symptoms might still be diagnosed with solely SZ, BD, or MDD, and not as having catatonia (as an independent diagnostic entity). The fact that all three diagnostic groups benefit from clozapine (complex neuropharmacological properties), benzodiazepines (e.g., lorazepam as a $GABA_A$ agonist), and electroconvulsive therapy [ECT; increase of GABA concentration in the medial prefrontal cortex (mPFC) [8]] suggests a *trans*-diagnosis mechanism of action with respect to the GABAergic system. Since there is convincing evidence from human studies that benzodiazepines and ECT modulate the GABAergic system, patients with SZ, BD and MDD may suffer from catatonia and GABAergic dysregulation. However, we are aware that the idea of one neurotransmitter as the basis for catatonia is oversimplified.

Second, case reports, MRI, and PET studies reported altered modulation of dopaminergic-based motor networks (e.g., increased dopaminergic turnover) driven by glutamate- and GABAergic nonmotor cortical networks, like default-mode network and sensory network in the pathophysiology of catatonia (for review see also [3, 9]). In particular, the cognitive control of negative emotions is modulated by $GABA_A$ receptors in various prefrontal regions, such as the orbitofrontal cortex (OFC) and mPFC [3]. Alterations of GABAergic neurotransmission/inhibition in the OFC and mPFC together with aberrant dopaminergic neurotransmission can lead to higher stress vulnerability, aberrant regulation of negative affect [10], and reduced behavioral control [2, 3]. From a neuropharmacological point of view, allosteric modulators at the $GABA_A$ receptor, such as lorazepam and zolpidem, have been shown to exert clinically beneficial effects on affective and motor catatonic symptoms. On the other hand, rapid withdrawal of clozapine or benzodiazepines often leads to an increase of potentially lethal malignant catatonic episodes [8]. Furthermore, baclofen overdose can lead to an increased $GABA_B$ receptor activity and abruptly worsen psychotic

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and catatonic symptoms and should therefore not be given to a patient suffering from SZ or catatonia [11].

Since catatonic symptoms often fluctuate, it is likely that catatonia is not exclusively caused by GABAergic system hypoactivity. In particular, consonant with Nair et al. and molecular models of catatonia, we suggest that this syndrome might be likely caused by a disbalance between $GABA_{A(decrease)}$ and $GABA_{B(increase)}$ receptor activity [12]. Furthermore, catatonic symptoms might be improved by dopamine/glutamate enhancing drugs (e.g., bromocriptine, dantrolene, acamprosate, amantadine). However, administration of dopamine blocking agents (e.g., antipsychotics other than clozapine, methyltyrosine, tetrabenazine, etc.) with a high dopamine receptor affinity (D_2-blockade) can worsen catatonic motor symptoms and lead to so called "drug-induced" catatonia [13]. On the other hand, valproate sodium blocks voltage-gated sodium channels, induces the expression of neuroprotective proteins, and increases brain GABA levels. The clinical efficacy of valproate sodium has been shown in BD and SZ patients presenting with prominent affective, aggressive, and impulsive symptoms, and we postulate that valproate sodium could stabilize GABAergic transmission and OFC activity. This could improve processing of negative stimuli and rebalance psychomotor activity in catatonia, although the exact molecular mechanism remains unclear.

But what makes the GABAergic system special is the fact that previous studies have been able to identify a dysfunction of the GABAergic system in patients with catatonia, regardless of their methodology (MRI, PET, pharmacological/intervention studies, case reports, etc.) and underlying diagnosis (SZ, BD, MDD, or autism). In particular, the application of benzodiazepines and ECT might increase the excitability of GABA-related inhibitory circuits and thereby facilitate the release of motor and behavioral catatonic symptoms. This notion is supported by the observation that both treatment strategies increase serum GABA levels and might improve symptoms of SZ, BD, MDD, and autism [14].

Although the efficacy of clozapine is based on its complex neuropharmacological properties and there is no evidence for clozapine's $GABA_B$ agonist activity in humans, we strongly suggest (not evident, but in accordance with Nair et al. [1]) that clozapine stabilizes aberrant fluctuation of $GABA_{A+B}$ activity (increase and decrease). The efficacy of clozapine in treatment-resistant SZ and catatonia supports this hypothesis.

In light of the above, we would appreciate hearing the authors' opinion on the relationship between $GABA_B$ receptor, clozapine and catatonia.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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