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PERSPECTIVE

From Inhibition of GABA-A Receptor-Mediated Synaptic Transmission by Conventional Antidepressants to Negative Allosteric Modulators of Alpha5-GABA-A Receptors as Putative Fast-Acting Antidepressant Drugs: Closing the Circle?

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Abstract: The present perspective paper shortly and specifically addresses the issues of whether inhibition of GABA-A receptor-mediated synaptic transmission may be involved in antidepressant-like actions and the therapeutic effects of conventional antidepressant (AD) drugs, and whether the recent development of negative allosteric modulators (NAMs) of the alpha5-GABA-A receptor may constitute significant progress in our knowledge on the neurobiology and the treatment of depression.

Keywords: GABA-A transmission, conventional antidepressants, antidepressant drugs, modulators of alpha5-GABA-A, GABA-A receptors, negative allosteric modulators.

1. INTRODUCTION

1.1. A Backward Perspective of Pharmacological GABA-A-Receptor Complex Inhibition and Antidepressant-Like Effects

Over thirty years ago, it was reported that repeated administration of different antidepressant drugs (ADs) decreased the binding of 3H-GABA to GABA-A sites in the mouse cerebral cortex and hippocampus [1], and the binding of 3H-flunitrazepam and 3H-βCCE (at the GABA-A/benzodiazepine(BZ)/chloride channel (Cl-) complex, or, GABA-A/BZ/Cl- complex) in whole rat brain [2, 3]. The *in vitro* addition of a wide variety of ADs (and active metabolites) from different chemical families was also shown to fully or partially reverse the GABA-inhibited binding of [35S]-t-butylbicyclophosphorothionate ([35S]TBPS, a ligand of the picrotoxin receptor, at the GABA-A-gated chloride channel) in rat brain membranes [4], and ADs of different neurochemical families reduced the cortical GABA-A-gated chloride channel conductance in rats, both *in vitro* [5] or following chronic systemic administration [6, 7].

These findings suggested that treatment with conventional ADs might reduce the functionality of the GABA-A receptor complex and raised the question of whether such a decrease in the function of the GABA-A receptor complex after chronic treatment with ADs of different pharmacological families could play a role in the therapeutic effects of these drugs. Accordingly, we, for the first time, reported that decreasing GABA-A-chloride channel function by co-administering sub effective doses of tricyclic ADs (imipramine –IMI-, desipramine –DMI-, clomipramine –CMI-) and subconvulsant doses of the chloride channel blockers picrotoxin (PIC) or pentylenetetrazole (PTZ) increased the anti-immobility effects of these ADs in the forced swimming test (FST) in rats, regardless of the treatment effects on motor activity (Table **1**) [7, 8]. Altogether, the above findings suggested that a reduction of GABA-A receptor complex function could play a role in the "therapeutic" effects of a number of AD drugs (having different primary neurochemical mechanisms of action).

Further support to that contention came from findings that other treatments leading to a reduction of GABA-A receptor complex function, such as chronic PTZ or prenatal diazepam, potentiated the anti-immobility effect of DMI in the FST [9, 10]. In addition, in the olfactory bulbectomy rat model of depression, cortical GABA-A receptors were found to be up-regulated, but they were normalised after chronic administration of the ADs clorgyline, paroxetine, or DMI [11]. Furthermore, the acute administration of negative allosteric modulators (*i.e.*, full or partial inverse agonists) of the benzodiazepine (BZ) receptor (at the GABA-A/BZ/Cl- complex), such as the β-carbolines β-CCE, harmane, norharmane, and harmine, was shown to have AD-like activity in the FST in rats or mice [12-14] (Table **1** shows the

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Table 1. Effect of the administration of sub-effective doses of tricyclic antidepressants (or the respective "vehicle"), combined with subconvulsant doses of PIC or PTZ, or administration of FG7142 (a non-selective partial inverse agonist of BZ receptors), on the time of immobility in the FST in rats.

-	**(1)**	-	-	**(2)**	-	-
-	**Vehicle**	**PIC0.5**	-	**Vehicle**	**PTZ15**	**PTZ25**
Vehicle	263.8 ± 9.1	282.2 ± 3.4	**Vehicle**	260.5 ± 7.7	260.6 ± 17.3	282.8 ± 7.4
IMI20	219.5 ± 17.5	192.8 ± 18.1 *	**IMI20**	187.5 ± 13.9 *	214.2 ± 17.6 *	121.4 ± 18.0 *,**
-	-	-	**DMI20**	245.5 ± 7.7	202.8 ± 18.8 *,**	**----**
-	**(3)**	-	-	**(4)**	-	-
Vehicle	257.4 ± 13.1	248.6 ± 10.7	**Vehicle**	287.4 ± 4.9	**----**	**----**
DMI30	218.1 ± 18.4	185.7 ± 17.4 *	**FG7142 (***)**	266.2 ± 7.0 *	**----**	**----**
CMI30 (***)	287.1 ± 3.7	239.5 ± 21.9**	-	**----**	**----**	**----**

Legend: It shows 3 representative studies **(1-3)** on the potentiation of the immobility-reducing effect of tricyclic antidepressants (administered at sub effective doses) by the concomitant injection of subconvulsant doses of the GABA-A negative modulators PIC or PTZ, and one study **(4)** on the effect of FG7142, a partial inverse agonist of BZ receptors. Means ± SEM of time of immobility (s) during the second swimming trial (duration 5 min) are also given. Animals used were male Sprague-Dawley rats weighing 360-450 g, which were counterbalanced for bodyweight across the different groups (n = 5-8 rats/group) in each study. IMI20, imipramine 20 mg/kg; DMI20, DMI30, desipramine 20-30 mg/kg; CMI30, clomipramine 30 mg/kg; PIC0.5, picrotoxin 0.5 mg/kg; PTZ15, PTZ25, pentylenetetrazole 15-25 mg/kg (all treatments were administered i.p.). The procedure of the FST was the classical one, as published by Porsolt *et al.* [42]. It consisted of 2 swimming trials; the first lasted 15 min and the second, administered 24 h later, lasted 5 min ([42]; see also [7, 8]). The observer was blind to the treatment received by the rats. **(1)** and **(2)**: These two studies involved 3 IMI or DMI injections (24, 5, and 1 h before the 2nd swimming trial of the forced swimming –FST- test) [42] and one injection of PIC or PTZ 20 min before the 2nd swimming trial. **(3):** This study involved 2 injections of each drug or vehicle: the first injection was given immediately after the first 15-min swimming trial, and the second injection was administered 60 (DMI, CMI, or vehicle) or 20 min (PIC or vehicle) before the second 5-min swimming trial. **(4):** This study involved two injections of FG7142 (or vehicle), the first 30 min before the first 15-min swimming trial (40 mg/kg) and the second (20 mg/kg) 30 min before the second 5-min swimming trial of the FST test (no behavioural differences between both groups were found in the first swimming trial; not shown). All drugs were dissolved in saline and administered i.p. *, $p < 0.05$ *vs*. Vehicle + Vehicle; **, $p < 0.05$ *vs*. "Antidepressant + Vehicle" (Duncan's multiple range tests following significant ANOVA, or Student's t-test in study 4). Results were taken from Fernandez-Teruel *et al.* [7], except for (***), which were previously unpublished results.

effects of FG7142, a partial inverse agonist of BZ receptors, or GABA-A-NAM).

In sum, the above evidence suggested that: 1) conventional AD drugs (most of them) reduce GABA-A receptor complex function, and this effect might be involved in their therapeutic effects, and 2) the reduction of GABA-A receptor complex function (by means of its negative allosteric modulation) might itself produce AD-like effects.

However, the precise identity and/or regional specificity of the GABA-A receptor subtype/s (or subunit/s) mediating these interactions with AD drugs remain unclear.

2. THE ADVENT OF AD-LIKE DRUGS ACTING AS NEGATIVE ALLOSTERIC MODULATORS (NAMS) AT THE ALPHA5-GABA-A RECEPTOR COMPLEX: INTERACTIONS WITH GLUTAMATE TRANSMISSION

It is conceivable that the troubling side effects linked to the non-selective negative modulation of GABA-A/BZ/Cl-receptor function (*e.g.*, proconvulsant activity, anxiogenesis) have precluded further development of these drugs as therapeutic possibilities. Recent molecular developments on GABA-A receptors have changed this scenario.

In fact, an outstanding development has been occurred in the characterization of the alpha5-containing GABA-A receptors (alpha5-GABA-A-Rs, or α5-GABA-A-Rs), which are a sub-type of GABA-A receptors that have more restricted distribution than other GABA-A receptor subtypes, and are particularly enriched in the hippocampus, prefrontal cortex, and olfactory bulb [15, 16]. It seems that the most common combination forming the α5-GABA-A-Rs is that of α5 subunit with β3 and γ2 subunits, leading to α5β3γ2 hetero-pentameric GABA-A receptors. Alpha5-GABA-A-Rs are sensitive to benzodiazepines, given that they contain the γ2 subunit. However, at variance with other GABA-A-R sub-types containing the γ2 subunit, α5-GABA-A/BZ-Rs display very low affinity towards imidazopyridines such as zolpidem (used for the treatment of insomnia) [16, 17]. Alpha5-GABA-A-Rs are mainly extrasynaptic and mediate tonic inhibition. The α5 subunit appears to be essentially absent at GABAergic synapses, which mediate phasic inhibition [16-19]. For instance, in the hippocampus, it has been found that α5-GABA-A-R activation reduces the activity of pyramidal neurons and neuronal networks, which could be involved in regulating hippocampus-dependent cognitive processes. In fact, selective negative allosteric modulators of α5-GABA-A-Rs have been found to improve various forms of associative and non-associative learning processes while being devoid of the proconvulsant and/or anxiogenic effects that are typically observed with non-selective GABA-A/BZ-R inverse agonists such as some beta-carbolines [16-18].

The finding of partial negative allosteric modulators (NAMs) acting specifically on BZ sites at these α5-GABA-A receptors has been particularly promising with respect to their possible utility in treating some psychiatric disorders or symptoms. Two of these NAMs with high selectivity for the α5-GABA-A/BZ-R are MRK-016 and L-655,708 [20, 21].

Importantly, following a single dose, both of them have been shown to restore the enduringly behavioral hedonic deficits and synaptic cortico-hippocampal deleterious effects induced by two chronic stress procedures, which model different aspects of depression in rats [21]. These findings were consistent with a previous study by Samardžić *et al.* [22], who demonstrated that L-655,708 had anti-immobility (*i.e.*, AD-like) effects in the FST in rats, although in this study, the rats received a repeated treatment with the drug [22].

The rapid AD-like action of MRK-016 has been further demonstrated in the FST and by its capacity to block the anhedonia produced by chronic restraint stress in mice [23]. Furthermore, along similar lines, Xiong *et al.* [24] have shown that, in the depression model of chronic social defeat stress (CSDS) in mice, MRK-016 showed antidepressant-like effects, as it reduced immobility in the TST and FST, as well as the deficit of sucrose preference produced by CSDS. Unexpectedly, L-655,708 did not produce AD-like effects in this study [24]. However, L-655,708 did produce an AD-like anti-immobility action in the FST in rats of both sexes, of similar magnitude to the effect of ketamine, which was dependent on the function of the ventral hippocampus [25, 26]. Consistently, it has been reported that the other two NAMs of the α5-GABA-A-R, namely RY-080 and PWZ-029, reduce immobility in the FST in mice [27].

Consistent with the above evidence, it is also striking that mice submitted to chronic stress showed a marked increase of α5 subunit mRNA expression in the frontal cortex [28]. In a related vein, mice submitted to CSDS exhibited increased α5-GABA-A-R protein expression in the hippocampus and prefrontal cortex while showing decreased α5-GABA-R protein expression in the nucleus accumbens [24]. Together with the finding that in depressed patients, there is an increase of α5-GABA-A-R protein expression in the parietal cortex [24], these findings seem to converge with the above pharmacological AD-like effects of NAMs of the α5-GABA-A-R, as well as with the notion that a decrease of α5-GABA-A-R function may lead to fast-acting AD-like actions and with the hypothesis that an increased function of these receptors might be related to depressive states [29].

Several antagonists of the glutamatergic N-methyl-D-aspartate (NMDA) receptor, such as ketamine, have fast-acting AD-like effects in rodents and humans [29, 30]. Similar to ketamine, it has been shown that MRK-016 promotes the coherence of cortical gamma frequency oscillations, which are related to activity-dependent synaptic potentiation and are thought to underlie the persistence of the behavioral effects for long periods after the substances eliminate completely from the central nervous system [23]. Remarkably, Zanos *et al.* have also shown that at variance with ketamine, MRK-016 does not produce psychotomimetic-like, locomotor stimulating, or attention-impairing effects [23]. It has been proposed that NMDA receptor inhibition by these NMDA receptor antagonists (*e.g.*, ketamine) would be mainly involved in their side effects, whereas subsequent NMDA receptor activation, perhaps involving NMDA receptors located on inhibitory GABAergic interneurons, would be responsible for their antidepressant action (*e.g.* [29]). Similarly, NAMs of the α5-GABA-A-R would inhibit these GABAergic interneurons, leading to disinhibition of glutamatergic neurotransmission preferentially in the PFC and hippocampus [23, 29]. Consistent with this notion, bocking glutamatergic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors before administration of ketamine or the α5-GABA-A-NAM MRK-016 prevents both the increase in frontocortical gamma powers (*i.e.*, gamma oscillations) and their antidepressant effects in the FST [23].

Several types of chronic stresses (which constitute validated models of depression in rodents) produce deleterious motivational/reward, emotional and cognitive depression-like effects. These are thought to be due (at least in part) to the alterations of excitatory synaptic function in brain areas related to these processes, such as the HC, PFC, and the nucleus accumbens [21]. Since α5-GABA-A receptors are particularly enriched in pyramidal cells of the HC and neocortex, the negative allosteric modulation of α5-containing GABA-A-Rs would be expected to promote coherent activity in these regions [21, 29]. In line with that, α5-GABA-A-NAMs, like conventional ADs, including the SSRIs and ketamine, have the capacity to restore these chronic stress-altered behavioural processes and excitatory synaptic strength and activity of cortico-mesolimbic pathways [21].

Some neurosteroids, such as brexanolone and zuranolone, appear to act as positive allosteric modulators (PAM) preferentially at extrasynaptic GABA-A receptors and synaptic GABA-A-Rs [18], and they exert anxiolytic and AD-like effects in rodent models. Brexanolone has been approved by FDA for the treatment of post-partum depression, a condition in which there is a down-regulation of extrasynaptic GABA-A receptors whose function might be normalized by the GABA-A-PAM [18]. How can this be reconciled with the AD-like actions of α5-GABA-A-NAMs discussed above? However, there seems to be no conclusive answer to this question. However, as mentioned earlier in this section, opposite to the down-regulation of extrasynaptic GABA-A-Rs in post-partum depression, an up-regulation of cortical α5-GABA-A-Rs has been reported in chronically stressed animals and depressed patients. It may be speculated that in both cases, *i.e.*, receptor down-regulation and up-regulation, the GABA-A-PAMs or GABA-A-NAMs may respectively help to normalize α5-GABA-A receptor function (and perhaps the disrupted inhibitory/excitatory balance in the HC and cortex) and thus the emotional/affective state.

In sum, α5-GABA-A-NAMs appear to display fast-acting AD-like actions while being devoid of the troubling side effects (*i.e.*, proconvulsant, anxiogenic, psychotomimetic) of the forementioned non-specific negative GABA-A modulators (PIC, PTZ, beta-carbolines) and NMDA antagonists (*e.g.*, ketamine). In addition, similarly to what has been proposed for NMDA antagonists, the AD-like effect of α5-GABA-A-NAMs may be due to the disinhibition of glutamatergic neurotransmission secondary to inhibition of GABAergic interneurons and to the fact that these actions occur preferentially in the hippocampus and frontal cortex.

3. SOME ARISING QUESTIONS AND FUTURE PERSPECTIVES: ARE WE CLOSER TO CLOSING THE CIRCLE?

The mechanisms of action of fast-acting ADs, whether they are NMDA antagonists or α5-GABA-A-NAMs, are

likely much more complex (and less understood) than those proposed above [29]. Other than the described effects on glutamatergic transmission, they may involve, for instance, changes in trophic factors (*e.g.*, BDNF), neuroplastic processes (*e.g.*, long-term potentiation, long-term depression), and changes in various downstream pathways [29].

However, it is remarkable that (i) decreasing GABA-A receptor-mediated synaptic transmission may potentiate the AD-like effects of some classical antidepressants [7-10] (as shown in Table **1**), (ii) classical BZ receptor inverse agonists (*i.e.*, non-selective NAMs such as anxiogenic β-carbolines) show AD-like activity following acute treatment [12-14] (as shown in Table **1**), and (iii) NAMs specific for the *α*5-GABA-A-R sub-type seem to exhibit fast-onset antidepressant-like effects (as reviewed in this paper). All these phenomena have in common that inhibition of GABA-A receptor function leads to AD-like (or to enhanced AD-like) effects.

The evidence discussed thus far in this article raises some questions that in turn may suggest some perspectives for research:

1. Given that, in addition to the above, the AD-like effects of conventional AD drugs are potentiated by NMDA antagonists [31-33], and that some of the behavioural effects of negative GABA-A modulators (*e.g.*, PTZ, FG7142) are mediated by NMDA receptors [34-41], the question arises that is glutamate transmission involved (and how?) in the potentiation of effects of conventional ADs by partially inhibiting GABA-A receptor function (as in the above-mentioned studies using PIC or PTZ at low doses)?
2. Is the potentiation of conventional AD drug effects by GABA-A receptor-negative modulators (*e.g.*, PIC, PTZ) mediated by *α*5-GABA-A receptors?
3. Would chronic administration of conventional ADs affect *α*5-GABA-A-R function? and would *α*5-GABA-A-NAMs interact with or potentiate the effects of conventional ADs?
4. Would the treatment with conventional ADs in combination with *α*5-GABA-A-NAMs enhance the effectiveness of each of these alone to produce antidepressant effects and prevent relapse?

It is conceivable that addressing these questions through pre-clinical research might provide some new clues about the neurobiological mechanisms of antidepressant action and depression, as well as about possible new drug combinations (for example, augmentation treatments) with greater efficacy for treatment.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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