



Neural basis for the ability of atypical antipsychotic drugs to improve cognition in schizophrenia

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Cognitive impairments are considered to largely affect functional outcome in patients with schizophrenia, other psychotic illnesses, or mood disorders. Specifically, there is much attention to the role of psychotropic compounds acting on serotonin (5-HT) receptors in ameliorating cognitive deficits of schizophrenia. It is noteworthy that atypical antipsychotic drugs (AAPDs), e.g., clozapine, melperone, risperidone, olanzapine, quetiapine, aripiprazole, perospirone, blonanserin, and lurasidone, have variable affinities for these receptors. Among the 5-HT receptor subtypes, the 5-HT_{1A} receptor is attracting particular interests as a potential target for enhancing cognition, based on preclinical and clinical evidence. The neural network underlying the ability of 5-HT_{1A} agonists to treat cognitive impairments of schizophrenia likely includes dopamine, glutamate, and gamma-aminobutyric acid neurons. A novel strategy for cognitive enhancement in psychosis may be benefited by focusing on energy metabolism in the brain. In this context, lactate plays a major role, and has been shown to protect neurons against oxidative and other stressors. In particular, our data indicate chronic treatment with tandospirone, a partial 5-HT_{1A} agonist, recover stress-induced lactate production in the prefrontal cortex of a rat model of schizophrenia. Recent advances of electrophysiological measures, e.g., event-related potentials, and their imaging have provided insights into facilitative effects on cognition of some AAPDs acting directly or indirectly on 5-HT_{1A} receptors. These findings are expected to promote the development of novel therapeutics for the improvement of functional outcome in people with schizophrenia.

Keywords: atypical antipsychotics, second generation, cognitive function, 5-HT receptors, lactate, energy metabolism, neuropsychology, electrophysiology

INTRODUCTION

Atypical antipsychotic drugs (AAPDs), sometimes called “second generation” antipsychotics, represent those exerting an antipsychotic efficacy at doses that do not cause extrapyramidal side effects (Meltzer, 1991, 2002; Sumiyoshi, 2008, 2013). With clozapine as the prototype, this class of agents includes risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, perospirone, blonanserin, paliperidone, iloperidone, asenapine, and lurasidone (Sumiyoshi, 2013). AAPDs share certain pharmacologic profiles in common, i.e., a relatively greater affinity for serotonin-5-HT_{2A} receptors relative to dopamine-D₂ receptors (Meltzer et al., 1989; Stockmeier et al., 1993; Sumiyoshi et al., 1995). In contrast, haloperidol, a typical antipsychotic drug (TAPD), shows a predominantly higher affinity for D₂ receptors compared to other receptors (Meltzer et al., 1989; Stockmeier et al., 1993; Sumiyoshi et al., 1995). In addition to the higher 5-HT_{2A}/D₂ binding affinity ratio, there are some minor differences among the AAPDs. For example, perospirone and aripiprazole show a relatively greater affinity for 5-HT_{1A} receptors, while lurasidone demonstrates a relatively high affinity for 5-HT₇ receptors (Sumiyoshi, 2013).

This paper provides a hypothesis regarding the neural basis for the ability of AAPDs to improve cognition. This theoretical issue is important from the perspective of the development of therapeutics for enhancing long-term outcome in patients with schizophrenia.

DO AAPDs ENHANCE COGNITION IN SCHIZOPHRENIA?

Typical antipsychotic drugs, such as perphenazine, have been reported to show some cognitive benefits in schizophrenia with a small effect size, as reported in the CATIE trial (Keefe et al., 2007). Importantly, Woodward et al. (2005) report an advantage of AAPDs over TAPDs in terms of enhancing cognition with a moderate effect size both in controlled and uncontrolled trials. However, there have been challenges to the pro-cognitive efficacy of AAPDs. For example, improvement of verbal memory by treatment with risperidone or olanzapine has been suggested to be no better than that of practice effect (or more precisely, test-retest effect) in normal controls (Goldberg et al., 2007). However, it may be premature to conclude that way, since no data were presented in that study (Goldberg et al., 2007) as to whether schizophrenia patients not receiving these AAPDs would have elicited the same degree of improvement as that in treated patients (Sumiyoshi, 2013).

One of the suggestions for this debate comes from the ability of lurasidone to dose-dependently improve cognitive functions, as measured by a computer-based test battery (Maruff et al., 2009), in a placebo-controlled double-blind study (Harvey et al., 2013; Sumiyoshi, 2013). This result provides a support for the ability of some AAPDs to enhance cognition in patients with schizophrenia, which is independent of a practice effect.

Another issue is what percentage of patients can be treated with a clinically meaningful degree. It is reported that a larger than 0.5 SD improvement in cognition substantially improves quality of life for patients (Norman et al., 2003). Accordingly, treatment with clozapine produced a significantly larger proportion of patients showing a larger than 0.5 SD improvement in letter fluency that predicts work outcome (Sumiyoshi and Meltzer, in preparation). Again, these findings provide a support for the proposition that AAPDs are superior over TAPDs for enhancing cognition.

In spite of these lines of evidence, cognitive benefits of AAPDs have been questioned, as noted above. One of the main reasons may be that the neural mechanisms for it have not been fully elucidated. Therefore, the following sections address this issue from the perspective of electrophysiological imaging, neural network, and energy metabolism.

ELECTROPHYSIOLOGICAL IMAGING

Figure 1 illustrates a rationale for electrophysiological approach toward cognitive assessment. The combination of neuropsychological and electrophysiological methods, e.g., event-related potentials (ERPs), may be beneficial for the understanding of mechanisms of cognitive enhancement, rational choice of psychotropic drugs, and prediction of functional outcome.

Specifically, we reported the effect of olanzapine on cognition and QOL, as well as P300, a component of ERPs, in patients with schizophrenia (Higuchi et al., 2008). P300 has been used as a marker of attentive cognitive processes. **Figure 2** (right) demonstrates P300 waveforms. At baseline, P300 amplitudes of patients were diminished compared to those of control subjects. After 6 month treatment with olanzapine, P300 amplitudes were increased, as were scores of verbal memory and quality of life (**Figure 2**, left).

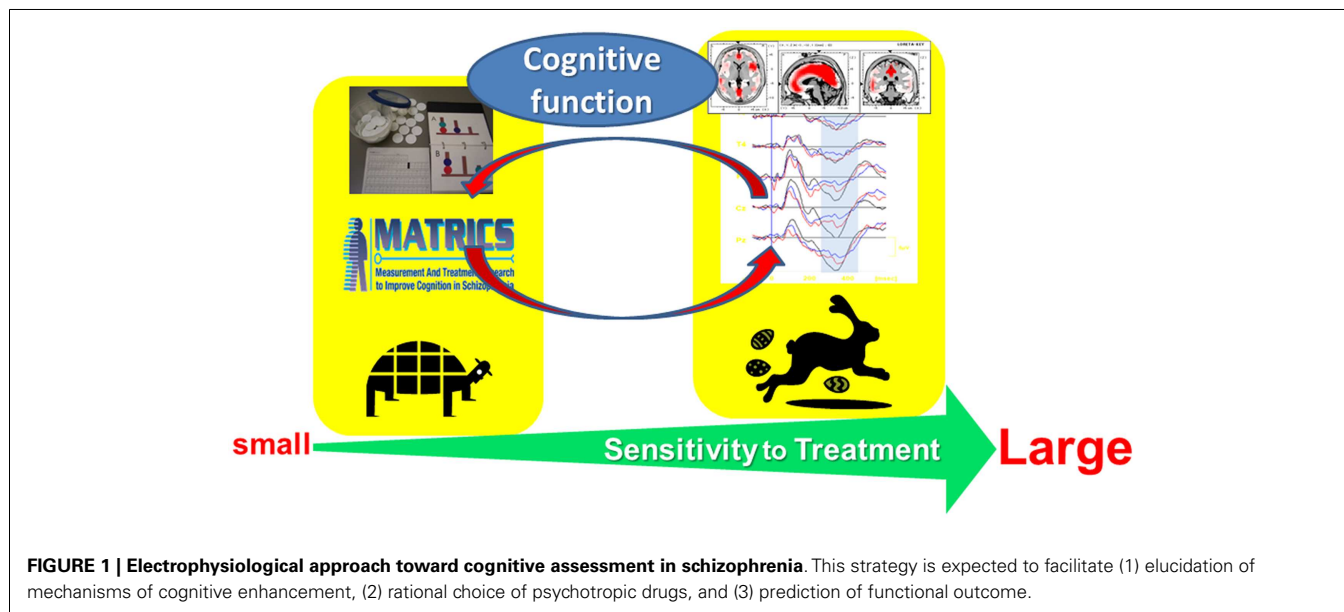
We subsequently evaluated the effect of olanzapine on P300 current source density in discrete brain areas (Higuchi et al.,

2008) (**Figure 3**). At baseline, P300 current density in the left superior temporal gyrus (STG) was decreased in patients. Olanzapine increased P300 current density in the left STG, but not other regions, such as the prefrontal cortex (PFC). In fact, this left-dominant pattern of P300 current density is similar to that for control subjects. These observations provide the first evidence that AAPDs ameliorate neurocognitive disturbances by correcting three-dimensional distribution of electrophysiological activity (Sumiyoshi et al., 2006, 2009; Higuchi et al., 2008).

An important aspect of this study was the correlation between the change in P300 current density and cognition or functional outcome. In fact, there was a significant positive correlation between improvement of verbal memory and enhancement of P300 current density in the left STG (**Figure 4**, right). Also, the change in the Quality of Life score (Heinrichs et al., 1984) was significantly correlated with enhancement of P300 current density in the left PFC (**Figure 4**, left). These results indicate that the change of regional electrophysiological activities in response to treatment can predict enhancement of cognitive and functional outcomes (Higuchi et al., 2008; Sumiyoshi et al., 2009, 2011).

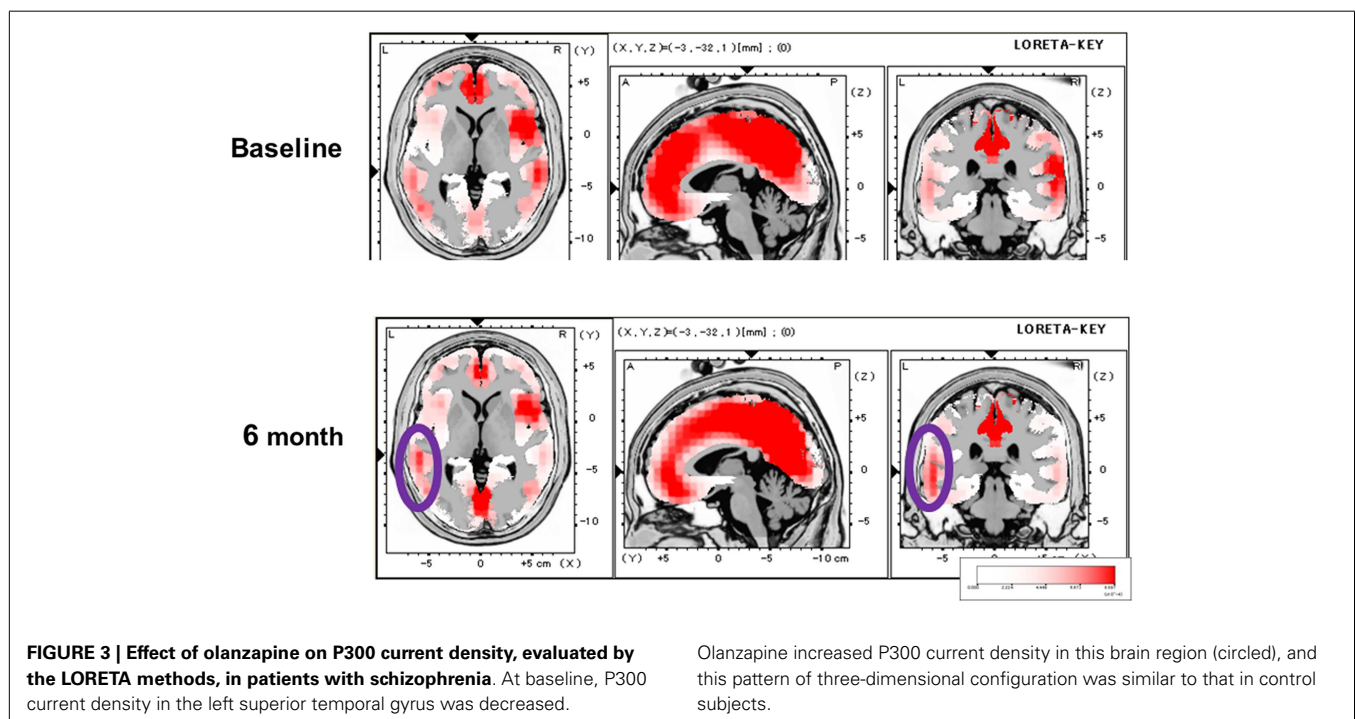
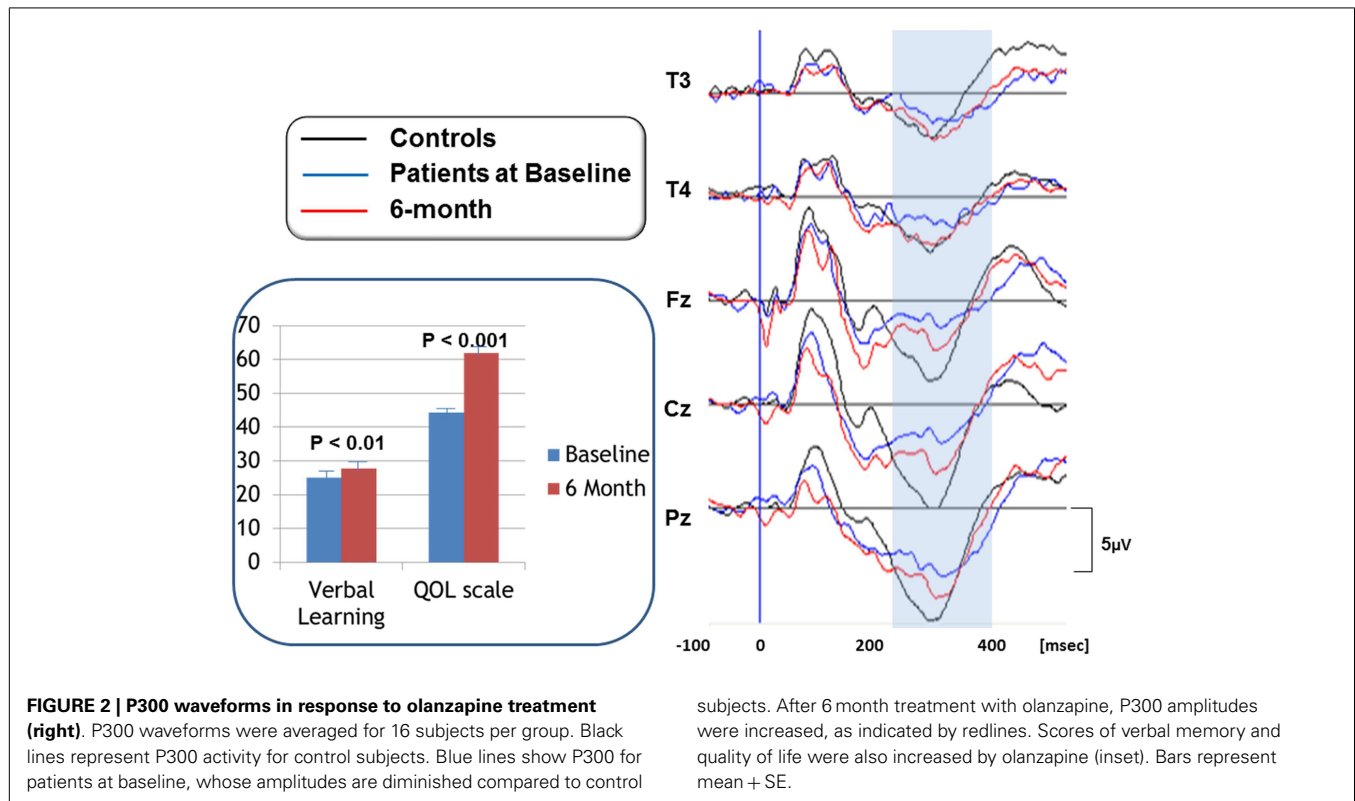
We also investigated the effect of perospirone on P300 current density (Sumiyoshi et al., 2009). Perospirone is one of the AAPDs marketed in Japan, and has high affinity for 5-HT_{1A} receptors (Araki et al., 2006; Sumiyoshi et al., 2009; Higuchi et al., 2013). Unlike the case for olanzapine, perospirone enhanced P300 current density in the left PFC in patients with schizophrenia (**Figure 5**). This change was correlated with improvement of cognitive function relevant to daily living skills (Sumiyoshi et al., 2009).

These observations are consistent with our previous report that 5-HT_{1A} receptor density is increased in the left PFC from subjects with schizophrenia (Sumiyoshi et al., 1996). The up-regulation of 5-HT_{1A} receptors is hypothesized to reflect a compensatory reaction to diminished neurotransmission through



these receptors (Sumiyoshi et al., 1996). The electrophysiological findings, mentioned here, may be consistent with this hypothesis, and explain distinct cognition-enhancing profiles of some AAPDs with high affinity for 5-HT_{1A} receptors, e.g., ziprasidone,

perospirone, aripiprazole, and lurasidone (Sumiyoshi, 2012, 2013, in press; Sumiyoshi and Higuchi, 2013). This concept may explain why perospirone, but not olanzapine enhanced P300 current density in the PFC.



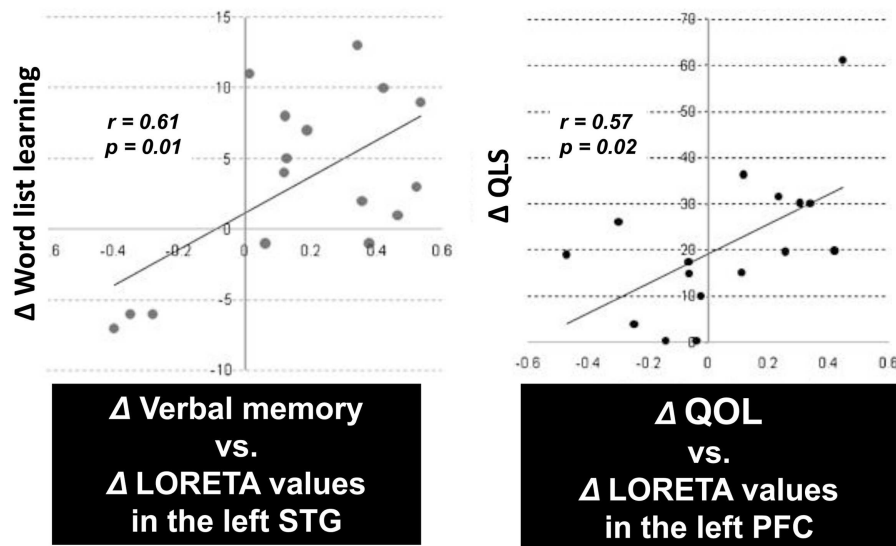


FIGURE 4 | P300 current density change vs. cognition/QOL changes in patients treated with olanzapine. There was a significant positive correlation between improvement of verbal memory and enhancement of

P300 current density in the left superior temporal gyrus (STG) (*left*). Also, the improvement of the Quality of Life score was correlated with enhancement of P300 current density in the left prefrontal cortex (PFC) (*right*).

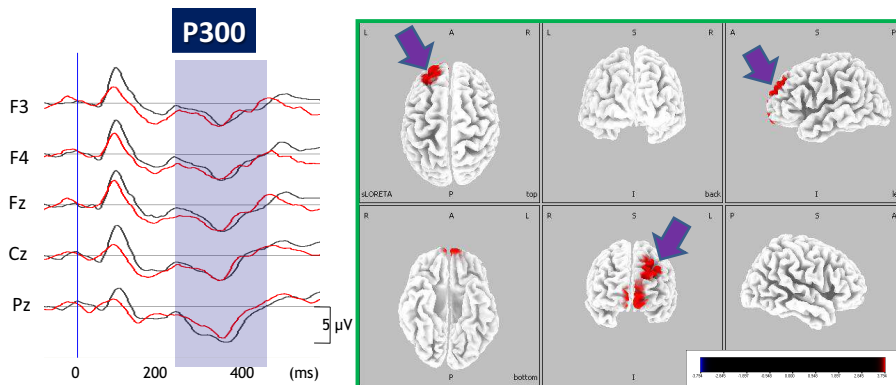


FIGURE 5 | Enhancement of P300 current density by perospirone in schizophrenia. *Left*, grand average of ERP waveforms before (black lines) and after (red lines) treatment with perospirone in patients with schizophrenia. *Right*, 6 months treatment with perospirone enhanced

P300 current density, evaluated by the sLORETA method, in the left superior frontal gyrus. Perospirone also improved social cognition, the degree of which was correlated with P300 activity in the frontal brain regions (see text).

NEURAL NETWORK MEDIATING COGNITIVE ENHANCEMENT OF AAPDs

As discussed, 5-HT_{1A} receptor agonism has been suggested to enhance cognition [see also Sumiyoshi et al. (2008)]. In fact, the addition of tandospirone, a 5-HT_{1A} partial agonist, improved executive function and verbal memory in patients treated with TAPDs (Sumiyoshi et al., 2001a,b) (Figure 6). Data from these clinical trials suggest 5-HT_{1A} agonists enhance some of the key cognitive domains, including those associated with frontal cortical function.

Figure 7 illustrates a neural network providing a possible basis for the ability of tandospirone and AAPDs acting on 5-HT_{1A} receptors to enhance cognition. Systemic administration of

5-HT_{1A} agonists has been shown to selectively stimulate 5-HT_{1A} receptors located on gamma-aminobutyric acid (GABA) interneurons in the PFC (Llado-Pelfort et al., 2011; Sumiyoshi and Higuchi, 2013). This diminishes the activity of GABA neurons, leading to disinhibition of Glu neurons. This may explain the ability of AAPDs to augment DA release in the PFC (Sumiyoshi and Higuchi, 2013), a putative mechanism for the ability of AAPDs to enhance cognition, in a 5-HT_{1A} receptor-dependent manner (Diaz-Mataix et al., 2005; Bortolozzi et al., 2010). These neural events may explain the ability of augmentation therapy with tandospirone to restore mismatch negativity amplitudes (Higuchi et al., 2010), an electrophysiological measure of glutamatergic activity that is diminished in schizophrenia (Javitt et al., 2008). Other possible

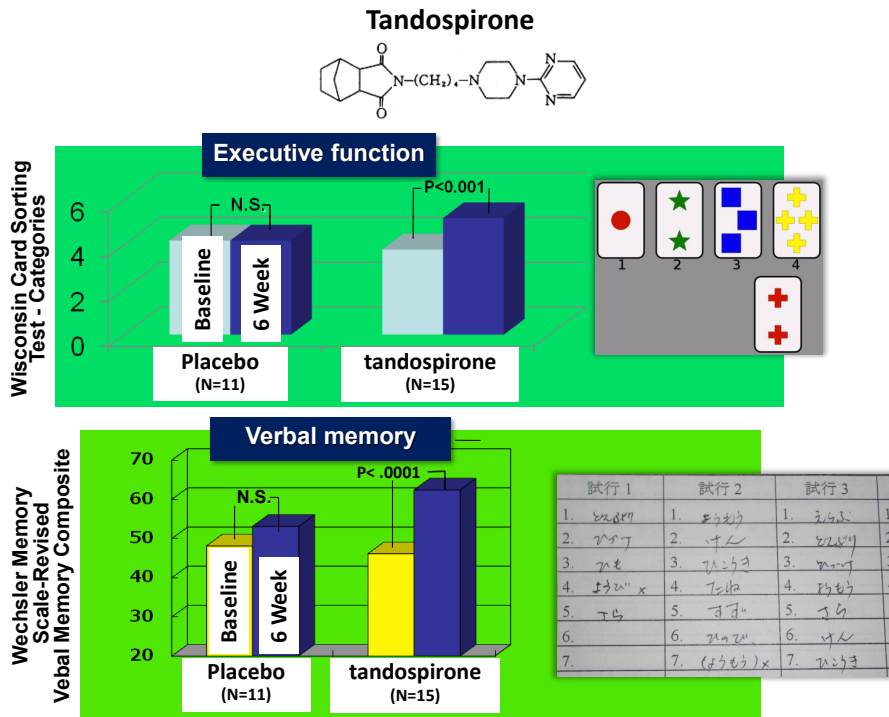


FIGURE 6 | Effect of tandospirone, a 5-HT_{1A} partial agonist, on cognition in schizophrenia. Six-week treatment with tandospirone, but not placebo enhanced executive function (effect size = 0.63) and verbal memory (0.70), two cognitive domains relevant to functional outcome, in patients receiving haloperidol.

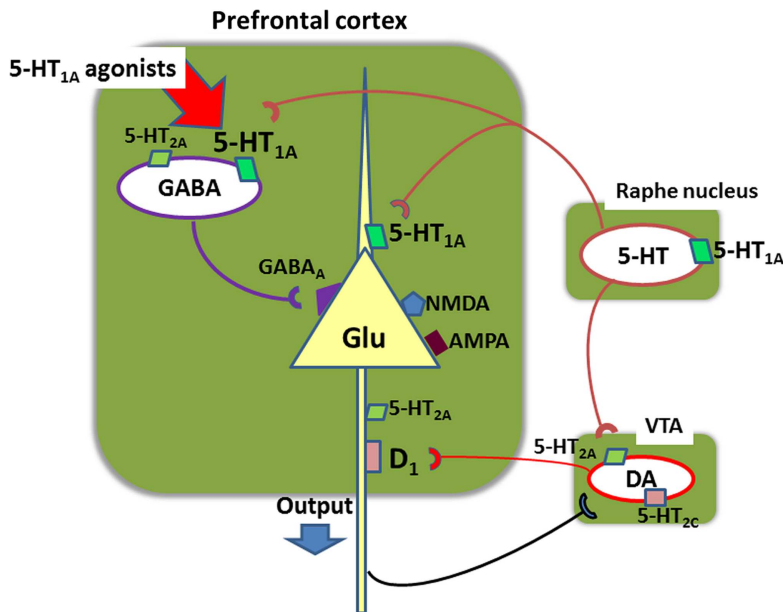


FIGURE 7 | Neural network in the prefrontal cortex involving glutamate (Glu), gamma-aminobutyric acid (GABA), serotonin (5-HT), and dopamine (DA) neurons. Systemic administration of 5-HT_{1A} agonists, such as 8-OH-DPAT, inhibits action potentials of GABA neurons, leading to disinhibition of glutamate neurons (Llado-Pelfort et al., 2011; Sumiyoshi and Higuchi, 2013). This also leads to activation of meso-cortical dopamine neurons. For example, administration of

clozapine, a 5-HT_{1A} agonist, increases extracellular DA concentrations in the prefrontal cortex in mice, but it does not occur in mutant mice lacking 5-HT_{1A} receptors (Bortolozzi et al., 2010). These neural events may explain the ability of augmentation therapy with tandospirone to restore mismatch negativity amplitudes (Higuchi et al., 2010), an electrophysiological measure of glutamatergic activity that is diminished in schizophrenia. VTA, ventral tegmental area.

mechanisms may involve GABA_B receptor-mediated transmissions (Gronier, 2008) or other neurotransmitters (e.g., acetylcholine).

ROLE FOR ENERGY METABOLISM

Traditionally, energy supply into the brain has been considered to depend on glucose. However, recent research suggests lactate plays a significant role in energy production both in the aerobic and anaerobic conditions, irrespective of the presence of glucose (Wyss et al., 2011; Uehara and Sumiyoshi, 2013).

The lactate-dependent energy metabolism has been associated with glutamatergic activity (Uehara et al., 2008). Specifically, glutamatergic transmissions enhance lactate production, which is mediated by *N*-methyl-D-aspartate (NMDA) receptors and glutamate transporters, as well as astrocytes (Uehara et al., 2008; Uehara and Sumiyoshi, 2013). Recently, lactate has been shown to exert neuroprotective effects (Wyss et al., 2011). These lines of evidence prompted us to use lactate metabolism as a biological basis for the effect of pro-cognitive drugs.

Measurement of lactate in the extracellular space can provide real-time information on its production (Uehara et al., 2008). Lactate metabolism was hypothesized to reflect energy supply in the brain areas crucial for cognitive functions, e.g., PFC. **Figure 8** describes the effect of tandospirone on extracellular lactate concentrations in a rat model of schizophrenia (Uehara et al., 2012). At the neonatal stage (postnatal days 7–10), rats were transiently administered MK-801, an antagonist at the NMDA receptor. In this experiment, these model rats showed suppression of the stress-induced increment of lactate levels in the PFC, suggesting impaired energy metabolism. This suppression in the model rats was inhibited by chronic treatment with tandospirone (once daily for 14 days

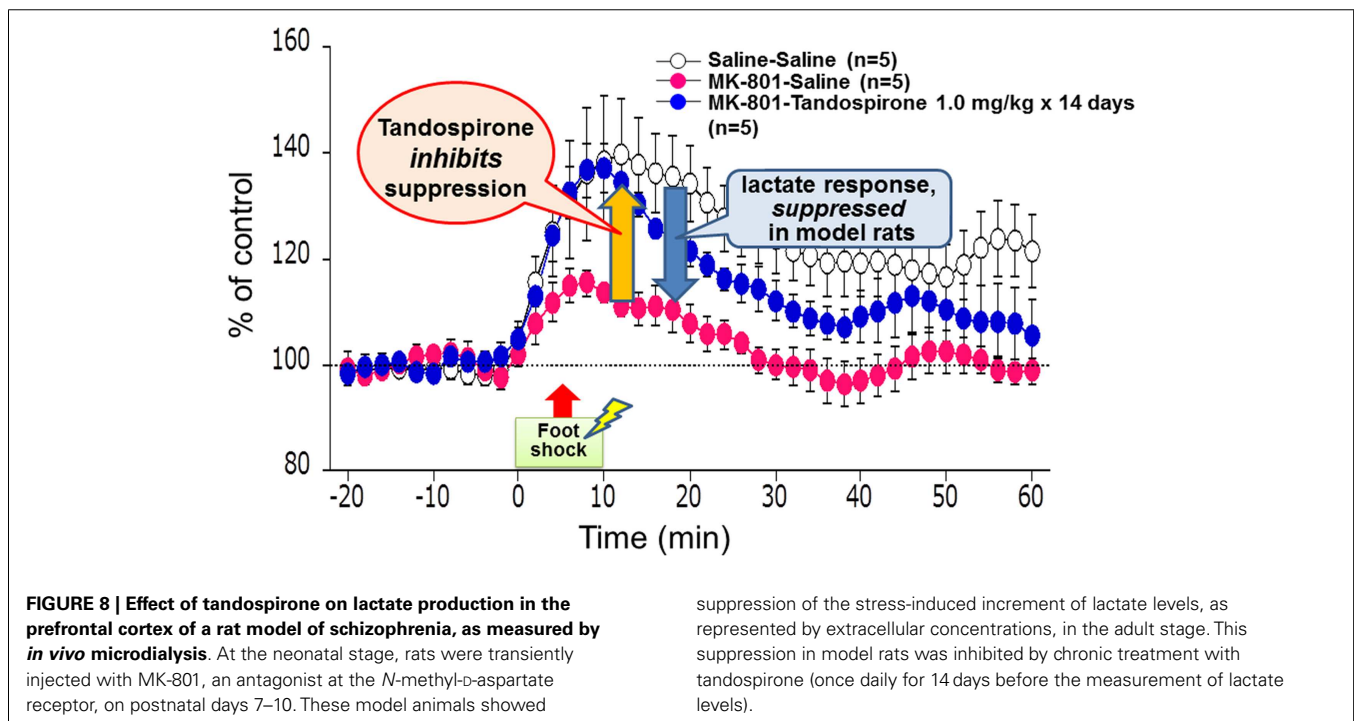
before the measurement of lactate levels) (Uehara et al., 2012). These results are consistent with clinical observations that 5-HT_{1A} agonists, such as tandospirone and buspirone, ameliorate cognitive impairment related to PFC function (Sumiyoshi et al., 2001a,b, 2007).

PERSPECTIVES

A main topic of this article has been the role for 5-HT_{1A} receptors in cognitive improvement. On the other hand, other 5-HT receptor subtypes have been suggested to be a potential candidate for cognitive enhancers. These include 5-HT₃ (e.g., mirtazapine, ondansetron), 5-HT₆ (Ro04-06790, Lu AE58054), and 5-HT₇ (SB25874, amisulpride, lurasidone) receptors [reviewed in Sumiyoshi and Higuchi (2013)].

Another issue to be considered in the development of promising agents is the assessment of functional outcome, in addition to neurocognition (neuropsychological performance, or “primary measures”). In this context, intermediate functional measures, or “co-primary measures,” have attracted interest as a target for therapeutic intervention (Sumiyoshi and Sumiyoshi, in press). For example, a greater sensitivity to treatment has been reported for co-primary measures compared to primary measures in a clinical trial of lurasidone and ziprasidone (Harvey et al., 2011). Therefore, intermediate functional measures (co-primary measures) deserve more attention in the development of novel pharmacotherapy for schizophrenia and related illnesses.

In conclusion, AAPDs have been shown to enhance cognition in a clinically meaningful manner. The mechanisms for it may include several modes of action and neural networks, which requires further explorations.



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