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# Serotonin-1A Receptors and Cognitive Enhancement in Schizophrenia: Role for Brain Energy Metabolism

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## 1. Introduction

Disturbances of cognitive function, evaluated by psychological and neurophysiological methods, have been shown to predict outcome in patients with schizophrenia (Green et al. 2000, Javitt et al. 2008, Sumiyoshi T. et al. 2011). In view of the paucity of treatment options to improve cognition for these patients, efforts to identify novel strategies are needed.

The prefrontal cortex (PFC) has been considered to regulate various aspects of cognitive abilities, e.g. working memory, memory organization, executive function, and attention (Sumiyoshi T. et al. 2011). Atypical antipsychotic drugs (AAPDs), eliciting cognitive benefits to some extent, enhance dopamine (DA) release in the medial PFC (mPFC), as demonstrated by in vivo microdialysis (Bortolozzi et al. 2010, Diaz-Mataix et al. 2005, Ichikawa et al. 2001). The ability of AAPDs to enhance DA in mPFC has been found to depend on serotonin (5-HT)-5-HT<sub>1A</sub> receptors, irrespective of direct in vitro affinity, based on observations from mutant mice lacking these receptors (Bortolozzi et al. 2010, Diaz-Mataix et al. 2005). This is consistent with behavioral observations that 5-HT<sub>1A</sub> partial agonists (e.g. tandospirone) and AAPDs with agonist actions on 5-HT<sub>1A</sub> receptors (e.g. perospirone, aripiprazole, ziprasidone, lurasidone) ameliorate memory deficits in rodent models of schizophrenia (Hagiwara et al. 2008, Horiguchi et al. in press, Meltzer et al. 2011, Nagai et al. 2009). Findings from electrophysiological studies suggest these cognitive benefits of 5-HT<sub>1A</sub> agonism are mediated by glutamate (Glu) and  $\gamma$ -aminobutyric acid (GABA) neurons (Higuchi et al. 2010, Llado-Pelfort et al. 2011).

In this chapter, the authors discuss the role for the key 5-HT receptor subtypes, i.e., 5-HT<sub>1A</sub>, 5-HT<sub>2A</sub>, 5-HT<sub>6</sub>, and 5-HT<sub>7</sub> receptors, in cognitive function in schizophrenia. Specifically, we will focus on several psychotropic/antipsychotic compounds stimulating 5-HT<sub>1A</sub> receptors, considered as one of the most promising candidates for cognitive enhancers (Meltzer et al. 2011, Newman-Tancredi and Kleven 2011, Newman-Tancredi and Albert in press). A hypothesis is presented on the relationship between cognition and lactate that provides an important energy substrate and reflects neural activity in the brain.

2. Neurocognitive deficits of schizophrenia

Schizophrenia has been characterized by positive symptoms (e.g. delusions, hallucinations and thought disorder) and negative symptoms (e.g. psychomotor retardation, affective flattening, social withdrawal, and alogia). Patients with the illness also exhibit a wide range of disturbances of cognitive function, including several types of memory, executive function (e.g. planning, monitoring, inhibition), vigilance, motor speed, and verbal fluency, with more than 1SD below the average of normal controls (Harvey and Keefe 1997).

Generally, they are considered to be independent of the psychotic symptoms. The cognitive deficits of schizophrenia have been investigated extensively as a determinant of functional outcome (Addington and Addington 2000, Green 1996, Green et al. 2000).

Several instruments to comprehensively assess cognitive function in schizophrenia have been developed. In particular, the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (Nuechterlein et al. 2008) (Fig 1) and the Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe et al. 2004) (Fig 2) are regarded to be qualified as international-standard neuropsychological tools in this respect. The authors have developed the Japanese versions of these cognitive test batteries (Kaneda et al. 2007, Sato et al. 2010), and have confirmed their sensitivity and validity to detect cognitive deficits in patients (Fig 3).

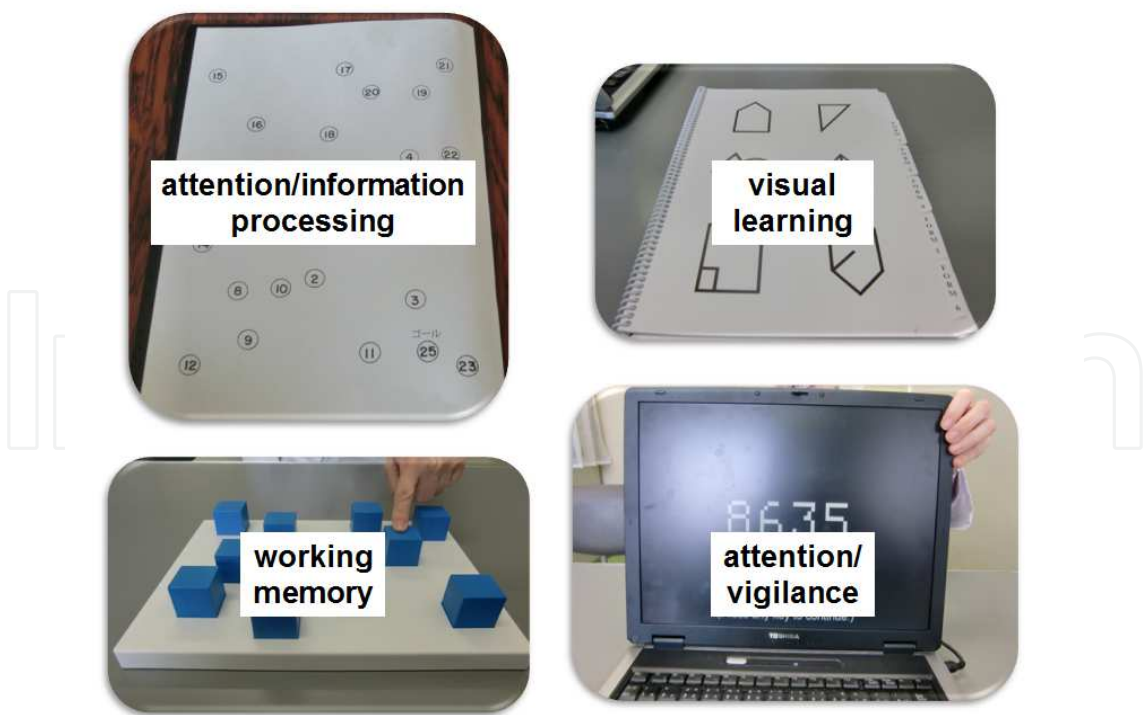


Fig. 1. Examples of tests from the MATRICS Consensus Cognitive Battery.

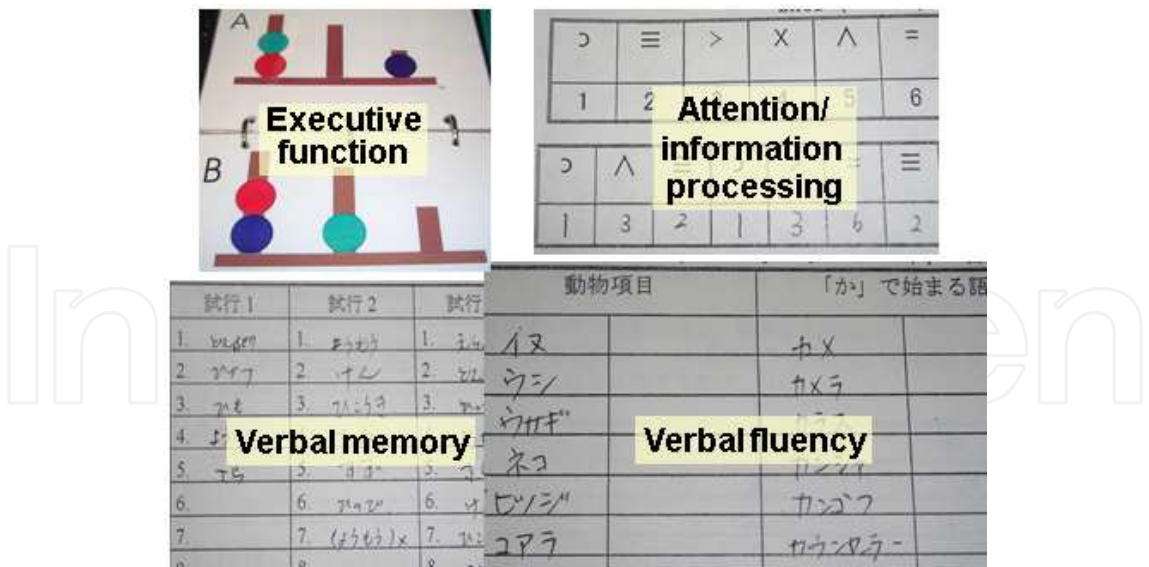


Fig. 2. Examples of tests from the Brief Assessment of Cognition in Schizophrenia.

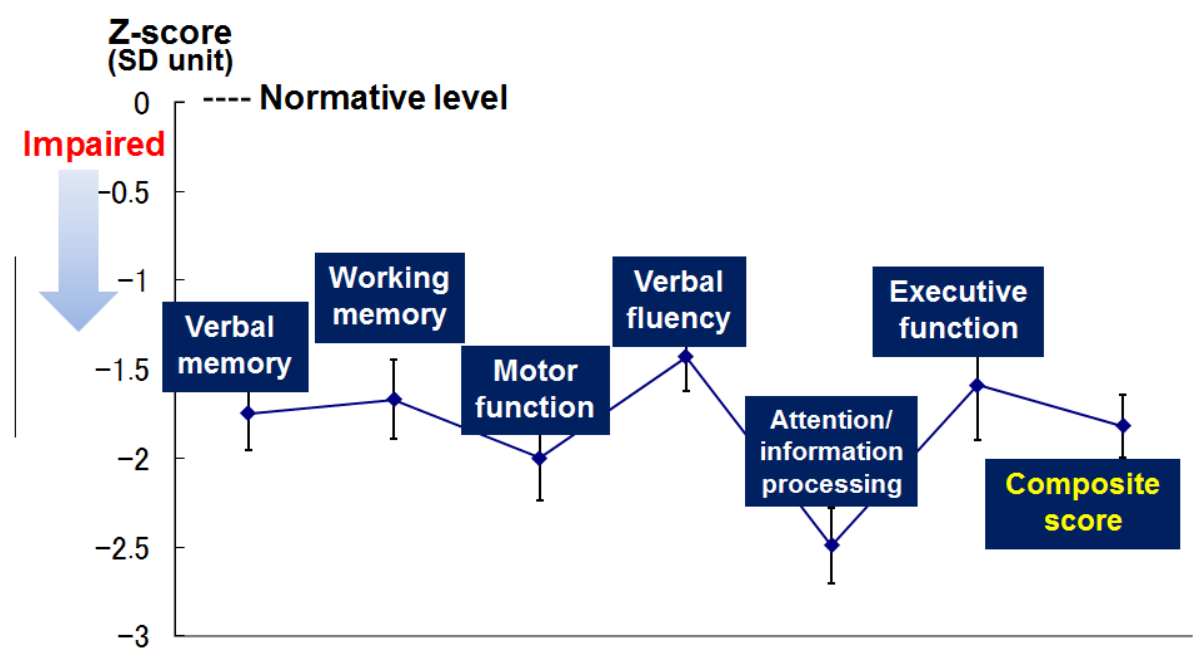


Fig. 3. Impaired cognitive function in schizophrenia as evaluated by the Brief Assessment of Cognition in Schizophrenia -Japanese Version (Kaneda et al. 2007).

3. 5-HT receptors and cognitive function

The role for several subtypes of 5-HT receptors in cognitive function has attracted interest, based, partly, on the distinct pharmacological properties of AAPDs, such as clozapine, risperidone, and olanzapine. For example, the ability of these agents to enhance DA and acetylcholine release in the mPFC, demonstrated by in vivo microdialysis, has been reported (Bortolozzi et al. 2010, Diaz-Mataix et al. 2005, Ichikawa et al. 2002, Ichikawa et al. 2001). Among the subtypes of 5-HT receptors (Fig. 4), 5-HT<sub>1A</sub>, 5-HT<sub>2A</sub>, 5-HT<sub>6</sub>, and 5-HT<sub>7</sub> receptors

have been shown to be associated with cognitive effects of AAPDs, suggesting pivotal roles for the serotonergic system in cognitive symptoms of schizophrenia (Sumiyoshi T. et al. 2007a, Meltzer and Sumiyoshi 2008, Sumiyoshi T. et al. 2008).

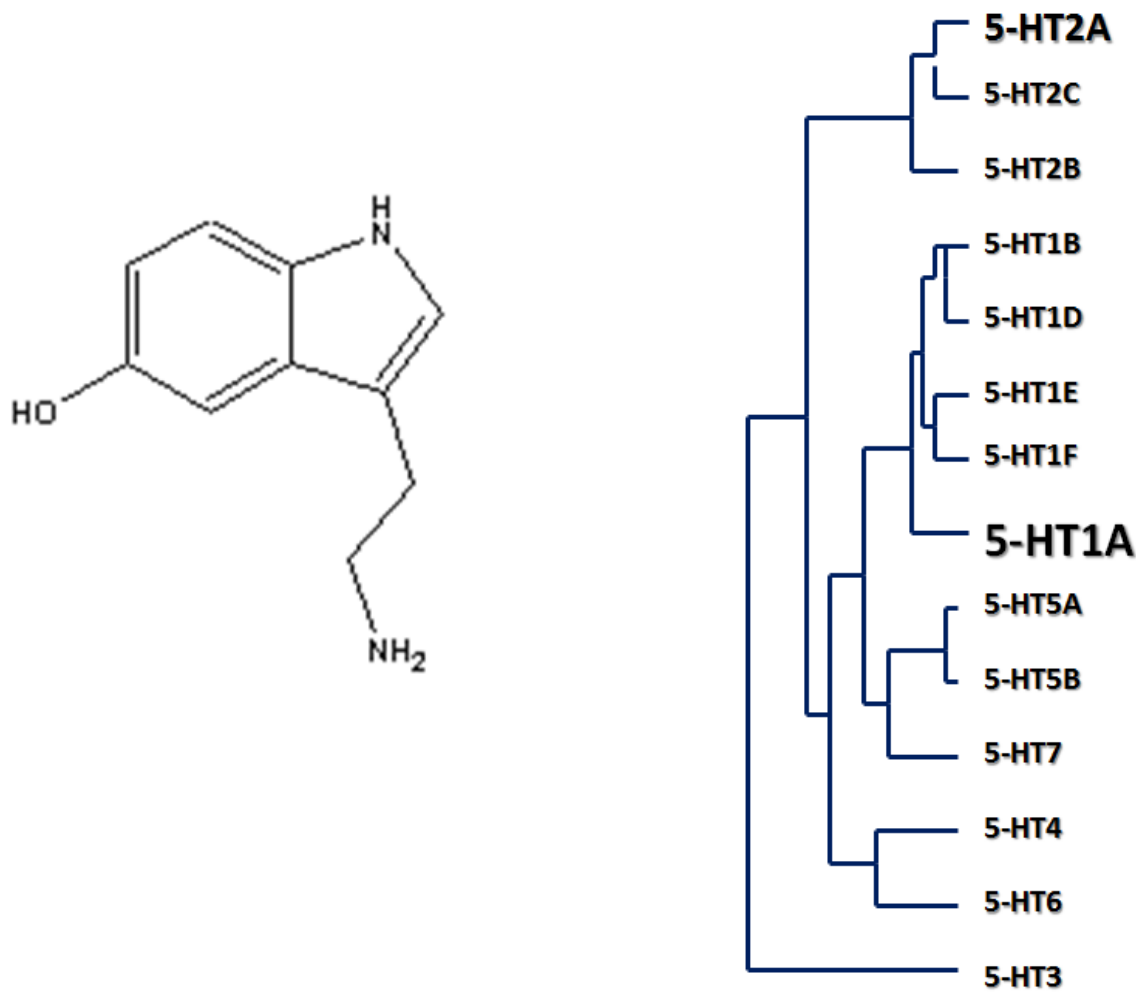


Fig. 4. Chemical structure of serotonin (5-HT) and its receptor subtypes.

Table 1. summarizes the mode of actions (agonism or antagonism) and specific compounds related to the above-mentioned 5-HT receptor subtypes. Among them, 5-HT<sub>1A</sub> receptor stimulation is currently considered as the most promising approach (Llado-Pelfort et al. 2011, Newman-Tancredi and Kleven 2011, Newman-Tancredi and Albert in press, Sumiyoshi C. et al. 2006, Sumiyoshi T. et al. 2008, Sumiyoshi T. et al. 2007a, Sumiyoshi T. et al. 2000, Sumiyoshi T. et al. 2007b, Sumiyoshi T. et al. 2001a, Sumiyoshi T. et al. 2001b, Sumiyoshi T. et al. 2009), as discussed in the next section. This is followed by 5-HT<sub>2A</sub> antagonism, as elicited by certain (although not satisfactory) efficacy of a series of AAPDs whose principal pharmacologic feature is blockade of 5-HT<sub>2A</sub> receptors (Meltzer et al. 1989, Meltzer et al. 2011, Meltzer and Massey 2011, Stockmeier et al. 1993, Sumiyoshi T. et al. 1995). Recent evidence from animal models of schizophrenia suggests the advantage of agonists at 5-HT<sub>6</sub> or 5-HT<sub>7</sub> receptors for ameliorating memory impairment, as revealed by behavioral experiments using antagonist at the N-methyl-D-aspartate (NMDA) type of Glu receptors (Horiguchi et al. 2011, Meltzer et al. 2011, Meltzer and Massey 2011).

5-HT subtypes	Mode of actions	Compounds
5-HT <sub>1A</sub>	(partial) agonist	tandospirone, buspirone F15599, ziprasidone aripiprazole, perospirone lurasidone
5-HT <sub>2A</sub>	antagonist	clozapine, risperidone olanzapine, perospirone quetiapine, melperone N-desmethylozapine
5-HT <sub>6</sub>	antagonist	Ro04-6790 Lu AE58054
5-HT <sub>7</sub>	antagonist	SB25874 amisulpiride lurasidone

Ref) Harvey et al. 2011; Kern et al. 2006; Llado-Pelfort et al. 2010, 2011; Meltzer et al. 2011; Meltzer and Massey 2011; Newman-Tancredi 2011, in press; Sumiyoshi et al. 2000, 2001a, 2001b, 2006, 2007a, 2007b, 2008, 2009

Table 1. Serotonin (5-HT) receptors in the treatment of cognitive disturbances.

4. Role for 5-HT<sub>1A</sub> stimulation in cognitive enhancement

The interest in the 5-HT<sub>1A</sub> receptor in relation to cognition in schizophrenia was founded by a series of pilot studies of the effects of augmentation therapy with tandospirone, a 5-HT<sub>1A</sub> partial agonist, in patients treated with antipsychotic drugs (Sumiyoshi T. et al. 2000, Sumiyoshi T. et al. 2001a, Sumiyoshi T. et al. 2001b). The addition of tandospirone (30 mg/day), but not placebo, to typical antipsychotic drugs (mainly haloperidol) for 4–6 weeks, was found to improve verbal memory (effect size = 0.70), memory organization, and executive function (0.63) (Sumiyoshi T. et al. 2000, Sumiyoshi T. et al. 2001a, Sumiyoshi T. et al. 2001b).

The beneficial effect of augmentation therapy with 5-HT<sub>1A</sub> agonists in schizophrenia was further supported by a randomly assigned placebo-controlled double-blind study with buspirone, another 5-HT<sub>1A</sub> partial agonist (Sumiyoshi T. et al. 2007a). Patients with schizophrenia, who had been treated with an atypical antipsychotic drug, were assigned to receive either buspirone, 30 mg/day, or matching placebo for 6 months. Buspirone outperformed placebo in improving the performance on a measure of attention/speeded motor performance (effect size = 0.32), indicating an advantage for cognitive abilities regulated by prefrontal cortex, as in the case of tandospirone. Evidence from these proof-of-concept studies has prompted the recent endeavor to develop cognition-enhancing drugs with 5-HT<sub>1A</sub> agonist actions (Depoortere et al. 2010, Llado-Pelfort et al. 2010, Llado-Pelfort et al. 2011, Newman-Tancredi 2010, Newman-Tancredi and Kleven 2011, Newman-Tancredi and Albert in press). Some of the compounds so far synthesized in this line are shown in Fig 5.



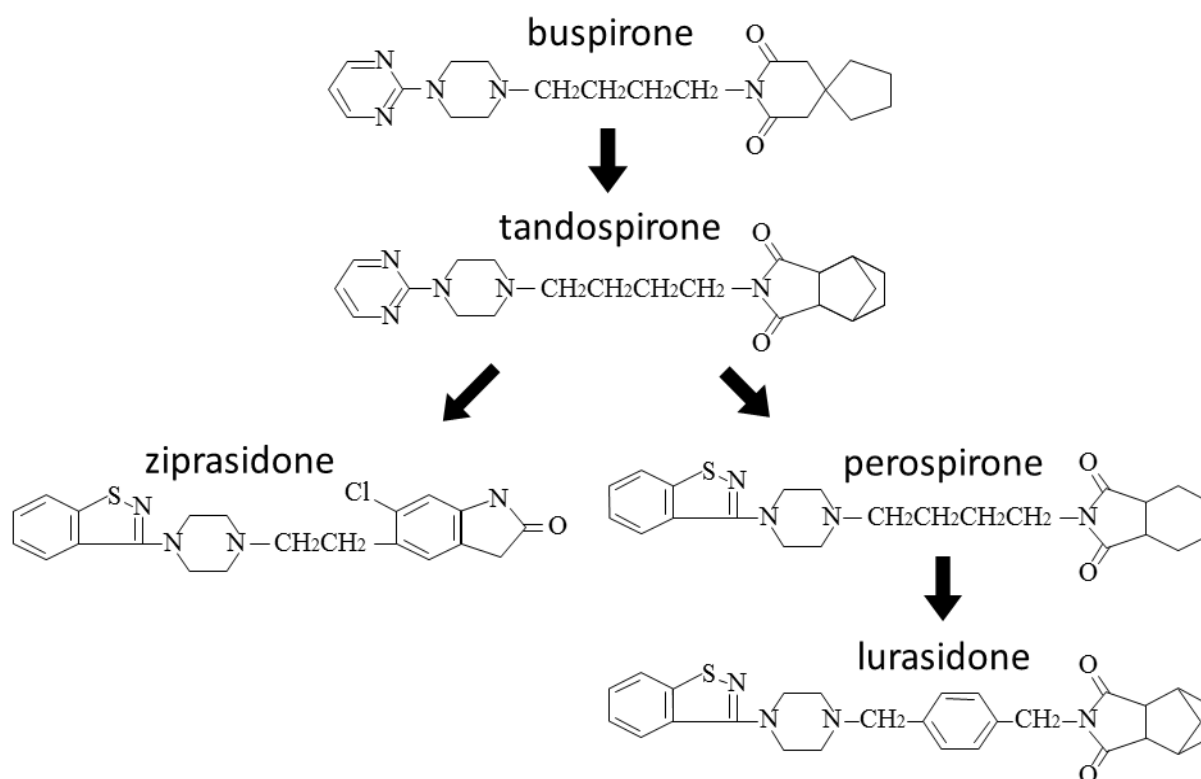
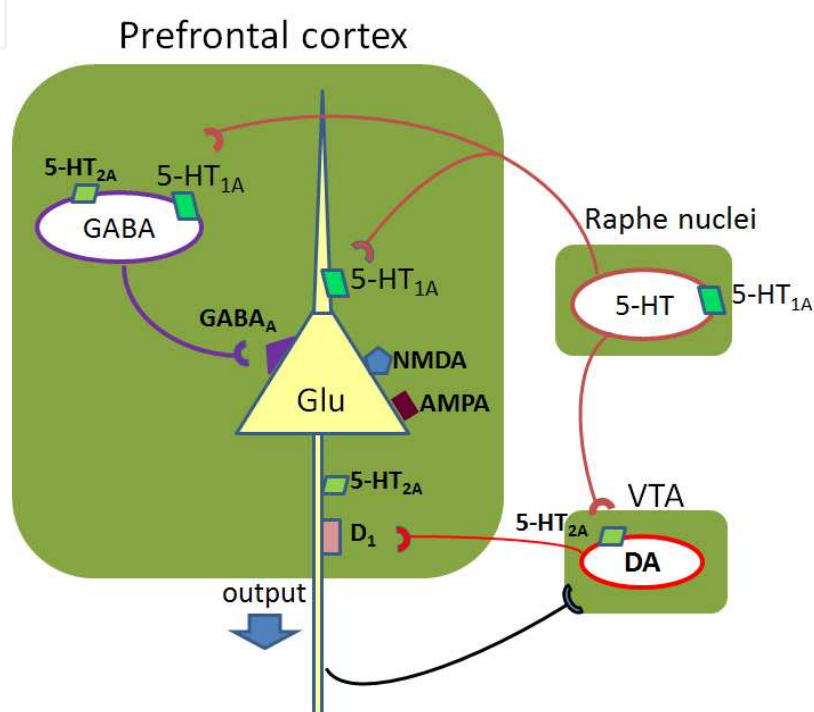


Fig. 5. Some of the psychotropic/antipsychotic compounds with agonist actions on 5-HT<sub>1A</sub> receptors.

Support for this therapeutic strategy comes from animal data suggesting 5-HT<sub>1A</sub> partial agonists (e.g. tandospirone) and AAPDs with agonist actions on 5-HT<sub>1A</sub> receptors (e.g. perospirone, aripiprazole, ziprasidone, lurasidone) ameliorate memory deficits due to NMDA receptor blockade (Hagiwara et al. 2008, Horiguchi et al. 2011, Horiguchi et al. in press, Meltzer et al. 2011, Nagai et al. 2009). The ability of these compounds to improve cognition has been related to enhancement of extracellular concentration of DA in the PFC (Bortolozzi et al. 2010, Diaz-Mataix et al. 2005, Ichikawa et al. 2001, Yoshino et al. 2004), an effect which is absent in mutant mice lacking 5-HT<sub>1A</sub> (Bortolozzi et al. 2010, Diaz-Mataix et al. 2005), but not 5-HT<sub>2A</sub> (Bortolozzi et al. 2010) receptors.

As illustrated in Fig. 6, Glu, GABA, 5-HT, and DA neurons constitute a network in the PFC that regulates several domains of cognition, e.g. some types of memory, executive function and attention. Among the variety of relevant receptors in this neural cascade, 5-HT<sub>1A</sub> receptors are located on Glu (pyramidal) and GABA neurons. Excitation of pyramidal neurons projecting to ventral tegmental area enhances mesocortical DA function, leading to amelioration of negative and cognitive symptoms of schizophrenia (Llado-Pelfort et al. 2010, Llado-Pelfort et al. 2011). Specifically, systemic administration of 8-OH-DPAT, a prototypical 5-HT<sub>1A</sub> agonist, to rats increased the discharge rate of pyramidal neurons in mPFC, by inhibiting fast-spiking GABAergic interneurons through a preferential action on 5-HT<sub>1A</sub> receptors on these latter neurons (Llado-Pelfort et al. 2011). This finding reconciles

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thought to be mediated by 5-HT<sub>1A</sub> receptors located on GABAergic interneurons regulating glutamatergic pyramidal neurons. VTA, ventral tegmental area.

though glucose has been considered to be a major supplier of energy in the brain, re-

Although glucose has been considered to be a major supplier of energy in the brain, recent investigations report that lactate also plays a significant role in energy metabolism, especially during acute neural activation (Aubert et al. 2005, O'Brien et al. 2007). According to the “astrocyte-neuron lactate shuttle hypothesis” (Laughton et al. 2007, Pellerin 2003), lactate is produced in a neural activity-dependent and glutamate-mediated manner by astrocytes, and is transferred to and used by active neurons (reviewed in Uehara et al. 2008) (Fig. 7). Data from a recent study (Wyss et al. 2011) suggest that the brain prefers lactate over glucose as an energy substrate when both are available, and that lactate exerts a direct neuroprotective effect.



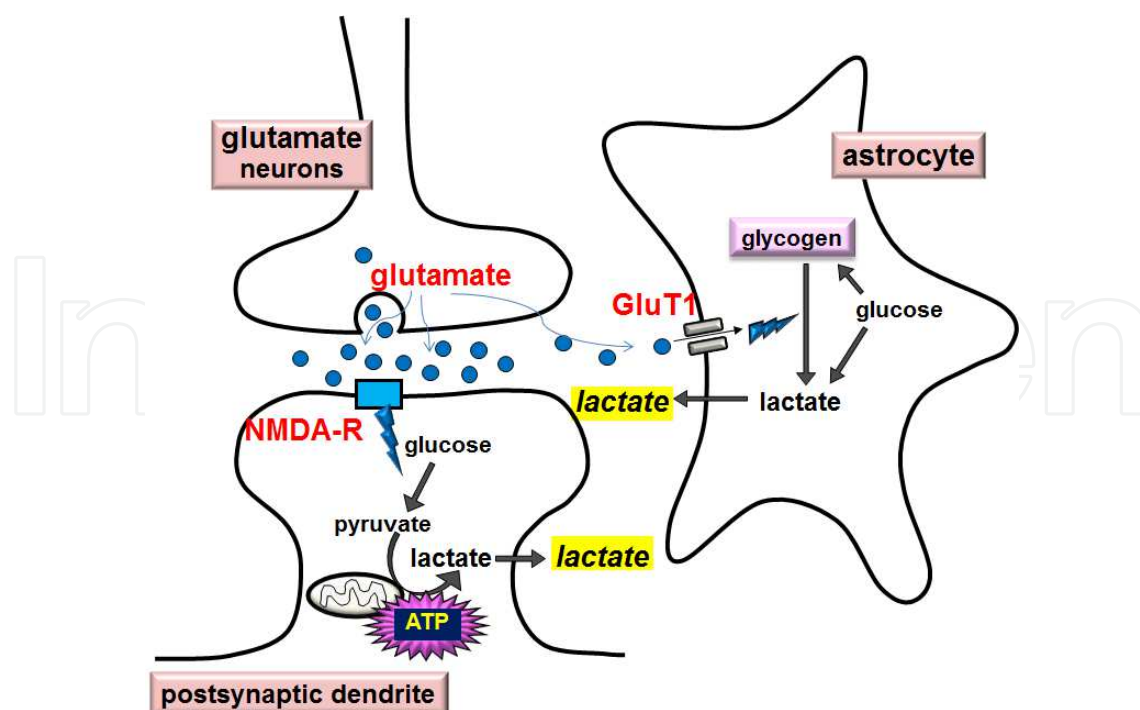


Fig. 7. Enhancement of lactate production by glutamatergic transmission. GluT1, glutamate transporter; NMDA-R, N-methyl-D-aspartate receptor. (Uehara et al. *Pharmacol Biochem Behav* 90:273, 2008)

## 6. Role for 5-HT<sub>1A</sub> agonism in lactate production in an animal model of schizophrenia

Rats administered MK-801 on postnatal days (PD) 7-10 have been shown to elicit impairment of set-shifting test, a measure of prefrontal cortex function, in early adulthood (Stefani and Moghaddam 2005). The same model animals elicit disruption of prepulse inhibition, a measure of sensorimotor gating (Uehara et al. 2009, Uehara et al. 2010) and enhancement of spontaneous and metamphetamine-induced locomotor activity (Uehara et al. 2010) after, but not before puberty (Table 2). These findings suggest that transient blockade of NMDA receptors at the neonatal stage produces cognitive abnormalities in rodent models of schizophrenia based on the neurodevelopmental hypothesis of the illness.

Lactate metabolism in mPFC has been shown to be modulated by 5-HT<sub>1A</sub> receptors both during resting condition and acute neural activation. In particular, acute administration of tandospirone led to a significant increase in extracellular lactate concentrations, and reduced the footshock stress-induced lactate increment in the mPFC in rats (Uehara et al. 2006). Taken together, it was hypothesized that transient blockade of NMDA receptors during the neonatal stage (modeling schizophrenia) would inhibit energy demands in response to stress in the mPFC at the young adult stage, and that 5-HT<sub>1A</sub> partial agonist, such as tandospirone, would reverse the effect of the neonatal insult on energy metabolism.

Female Wistar rats obtained at 14 days of pregnancy. At postnatal (PD) day 7 (PD7), male pups were randomly divided into two groups. They received MK-801 (dizocilpine), or an

equal volume of saline (control; vehicle group) once daily for 4 days. At the time of weaning on PD 21, the pups were grouped into four to six per treatment.

MK-801			
▼▼▼			
Postnatal days	7-10	35	63
Puberty			
Prepulse inhibition		N.C.	decreased
Spontaneous locomotion		N.C.	↑
MAP-induced locomotion		N.C.	↑

Transient blockade of NMDA receptors by MK-801 at the neonatal stage produces disruption of prepulse inhibition, as well as spontaneous or methamphetamine (MAP)-induced hyperlocomotion after, but not before puberty.  
N.C., no change.

Table 2. Behavioral changes in a rat model of schizophrenia based on the neurodevelopmental hypothesis.

On PD49, animals were assigned to receive either saline or tandospirone at 1.0 mg/kg, (s.c.). This yielded the following groups: saline-saline group, saline-tandospirone group, MK801-saline group, and MK801-tandospirone group. For 14 days before the microdialysis examination, saline or tandospirone was administered (s.c.) once daily. Microdialysis was performed 24 hours after the last injection.

Microdialysis experiments were performed on PD63. Forty-two to 48 hr before microdialysis experiments, the animals were anesthetized, and were mounted on a stereotaxic apparatus. A dialysis probe was implanted into the left mPFC with the coordinates of A 3.2mm, L 0.6mm, V 5.2mm from bregma. The dialysis experiment was carried out on the freely moving rats. Artificial CSF was perfused into the dialysis probe. The dialysates were mixed on-line with an enzyme solution containing L-lactate dehydrogenate and NAD<sup>+</sup> in a T-tube. During transport of the mixture to the fluorometer, lactate was enzymatically oxidized and the fluorescence of the nicotinamid adenosine dinucleotide diphosphate (NADH) formed was continuously measured, with a standard solution of 100 μmol/L lactate for calibration.

Footshock stress was administered using a plastic communication box, according to the method described previously (Uehara et al., 2006). The box (L 51cm x W 51cm x H 40cm) was equipped with a grid floor, and was subdivided into nine compartments (17cm x17cm) by transparent plastic walls. In this study, we used 4 compartments area (34cm x 34cm) for the field of free moving and footshock administration. The communication box was connected to a shock-generator to deliver footshocks as described below. Each footshock session consisted of a scramble shock of 0.3 mA for 5 seconds administered every 30 seconds for 10 minutes. After the experimental sessions, the position of dialysis probes was verified by dissection of the brain.

Data were analyzed by analysis of variance (ANOVA). The average of extracellular lactate concentrations during the period preceding the start of footshock stress (ten measurements performed every 2 min) was used as the control value (100 %). Data from tandospirone administration experiments were analyzed using three-way repeated measures ANOVA; Status and Drug were treated as between-group variables. Time was treated as a repeated measures variable.

As expected, transient neonatal administration of MK-801 suppressed lactate increment in response to footshock stress around puberty, which was reversed by 14-day treatment with tandospirone (Fig. 8). Further, the ability of tandospirone to ameliorate the response of lactate production in model animals was abolished by co-administration of WAY-100635, a selective 5-HT<sub>1A</sub> antagonist (Uehara et al., in press).

These findings are consistent with clinical observations that perospirone and tandospirone improved cognitive abilities governed by the PFC, coupled with enhancement of electrophysiological activities in this brain region, in patients with schizophrenia (Higuchi et al. 2010, Sumiyoshi T. et al. 2009). Translational approach, like this, is expected to provide a novel insight into the development of therapeutics targeting cognitive disturbances of schizophrenia.

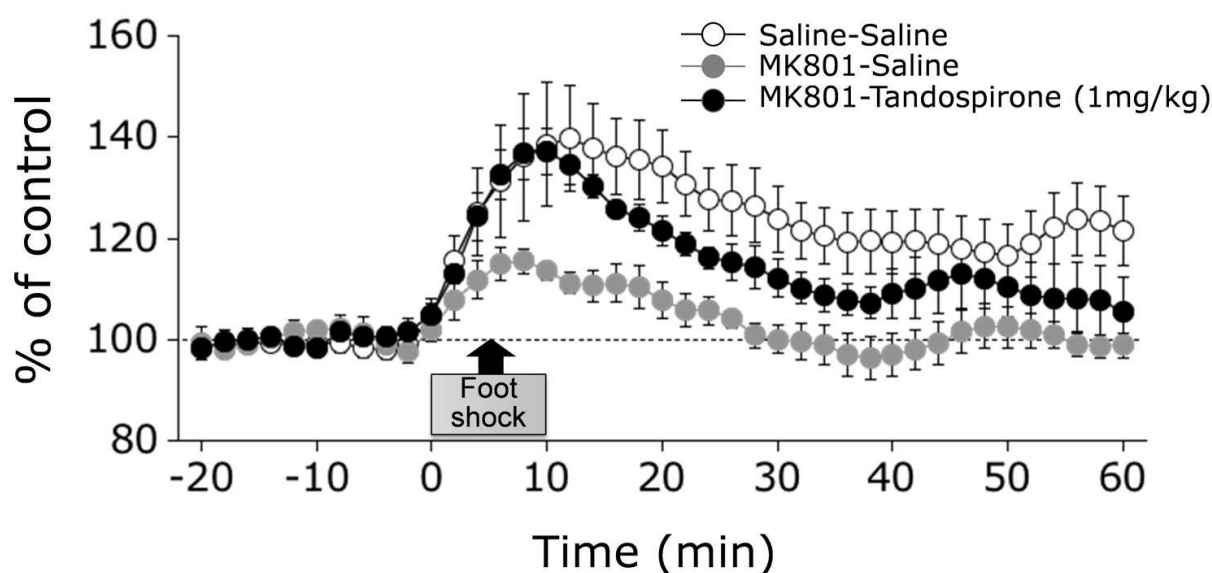


Fig. 8. Extracellular concentrations of lactate in the medial prefrontal cortex in young adult rats. Transient blockade of NMDA receptors by MK-801 at the neonatal stage (modeling schizophrenia) suppresses lactate increment in response to footshock stress (saline-saline vs. MK-801-saline). Treatment with tandospirone, a 5-HT<sub>1A</sub> partial agonist, for 14 days reverses the decrease in lactate production in the model animals (MK-801-saline vs. MK801-tandospirone). A significant main effect of tandospirone in MK-801-treated animals was noted ( $F(1,8)=12.94$ ,  $P=0.007$  by ANOVA).

## 7. Conclusions

Behavioral, neurochemical and electrophysiological data indicate 5-HT<sub>1A</sub> agonists improve negative symptoms and cognitive deficits of schizophrenia. Specifically, compelling evidence suggests that the cognitive benefits of 5-HT<sub>1A</sub> agonism are mediated by Glu and

GABA neurons (Higuchi et al. 2010, Llado-Pelfort et al. 2011). The role for 5-HT<sub>1A</sub> receptors in cognitive enhancement has been suggested by imaging genetics data regarding brain energy metabolism (Sumiyoshi T. et al. 2008) and by pharmacogenetics investigations (Sumiyoshi T. et al. 2010) [reviewed in (Newman-Tancredi and Kleven 2011, Newman-Tancredi and Albert in press)]. Findings from translational research, herein presented, are expected to facilitate the development of novel therapeutics for cognitive impairment in schizophrenia and other psychiatric disorders.

## 8. Acknowledgement

This work was supported by Health and Labour Sciences Research Grants and grants from Japan Society for Promotion of Sciences.

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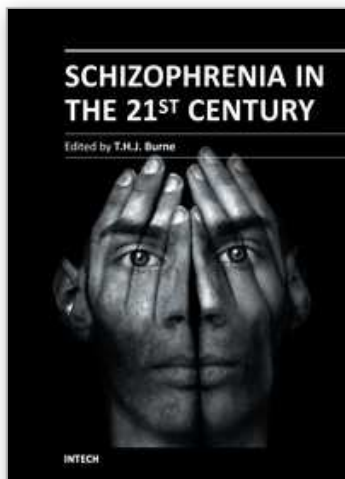
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## **Schizophrenia in the 21st Century**

Edited by Dr. T.H.J. Burne

ISBN 978-953-51-0315-8

Hard cover, 180 pages

**Publisher** InTech

**Published online** 23, March, 2012

**Published in print edition** March, 2012

Schizophrenia is a poorly understood but very disabling group of brain disorders. While hallucinations and delusions (positive symptoms of schizophrenia) feature prominently in diagnostic criteria, impairments of memory and attentional processing (cognitive symptoms of schizophrenia) are attracting increasing interest in modern neuropsychiatry. Schizophrenia in the 21st Century brings together recent findings on this group of devastating disorders. We are still a long way from having effective treatment options, particularly for cognitive symptoms, and lack effective interventions and ways to prevent this disease. This volume covers various current options for therapy, clinical research into cognitive symptoms of schizophrenia and preclinical research in animal models.

### **How to reference**

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Tomiki Sumiyoshi and Takashi Uehara (2012). Serotonin-1A Receptors and Cognitive Enhancement in Schizophrenia: Role for Brain Energy Metabolism, Schizophrenia in the 21st Century, Dr. T.H.J. Burne (Ed.), ISBN: 978-953-51-0315-8, InTech, Available from: <http://www.intechopen.com/books/schizophrenia-in-the-21st-century/brain-energy-metabolism-and-cognitive-enhancement-in-psychosis>

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