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Molecular mechanisms underlying synergistic effects of SSRI–antipsychotic augmentation in treatment of negative symptoms in schizophrenia

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Abstract Negative symptoms in schizophrenia respond poorly to antipsychotics, but may improve when these are augmented with selective serotonin reuptake inhibitors (SSRIs). The molecular mechanisms underlying the augmentation are unclear. Nevertheless, significant progress has been made, pointing to some candidate systems which may be involved in SSRI–antipsychotic synergism. Thus, the enhanced dopamine release by SSRI–antipsychotic treatment is modulated by specific serotonergic receptors and by tyrosine hydroxylase. There are modifications in gamma-aminobutyric acid system via glutamate decarboxylase 67, protein kinase C beta and the receptor for activated C-kinase 1 (Rack1). Some studies indicate the input of transcription and neurotrophic factors as phospho-cyclic adenosine monophosphate response element-binding protein, Fos and fibroblast growth factor-2. Alterations in calcium signaling (neurogranin, regulator of G-protein signaling and Rack1) and in cytokine receptors for interleukin-8 and chemokine have also been reported. While as yet limited in scope, the evidence suggests definable molecular targets which may be implicated in drug development based on SSRI–antipsychotic synergistic actions.

Keywords Schizophrenia · Negative symptoms · Selective serotonin reuptake inhibitors · Antipsychotic drugs · GABA · Cytokines

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Introduction

Augmentation strategies in psychiatric disorders

Psychiatric disorders, such as schizophrenia, major depression, bipolar illness and obsessive-compulsive disorders (OCD), are characterized by a wide range of behavioral, emotional and cognitive abnormalities (Andreasen et al. 1994; Berman et al. 1997; Dell'Osso et al. 2007). This complex symptomatology often necessitates the use of more than one drug and many combinations of psychotropics have been tried in attempts to improve the clinical response of patients. Over the years, it has become evident that some combinations do induce a favorable clinical response, not achieved by each of the drugs given alone (Fava 2001; Silver 2001). Currently, the choice of drug combinations is based on a trial and error paradigm guided by clinical response. Understanding the biological principles, by which the combined treatments act, would enable a more "rational" selection of drugs and provide insights into the pathological mechanisms of the disorders.

This review stems from our interest in augmentation strategies, in particular the combination of selective serotonin reuptake inhibitor (SSRI) with antipsychotic drug. Our focus is on the use of this combination for treatment of

negative symptoms of schizophrenia, although it has also been found effective in other psychiatric conditions (Table 1). While there is considerable research into the mechanisms of action of individual antipsychotic and antidepressant drugs, few studies examined the mechanism of augmentation strategies, hence there is a lack of a theoretical framework to guide research in this field. Our aim is to review the evidence for the synergistic effects of SSRI–antipsychotic treatment at clinical, biochemical and molecular levels and identify molecular targets which may mediate them and underlie the clinical effects.

Selective serotonin reuptake inhibitor–antipsychotic therapy for negative symptoms in schizophrenia

Schizophrenia is a chronic, disabling brain disorder comprising symptoms which can be classified into two groups: 'positive symptoms' (hallucinations and delusions) and 'negative symptoms' (apathy, anhedonia, flat affect, avolition and social withdrawal). Negative symptoms in particular are a challenge to available treatments. Thus, typical neuroleptics are effective against positive but not negative symptoms and the success of the newer generation, "atypical" drugs, is limited (Burton 2006). Augmentation of antipsychotic drugs with SSRI antidepressants may be a useful strategy for targeting negative symptoms as shown in controlled studies on addition of fluvoxamine to typical antipsychotic drug (Rummel et al. 2006; Silver et al. 2000; Silver and Nassar 1992; Silver and Shmugliakov 1998) and in open studies and case reports on augmentation of atypical drugs (clozapine and olanzapine) (Chaichan 2004; Hiemke et al. 2002; Lammers et al. 1999; Silver et al. 1995; Szegedi et al. 1999).

The mechanism of SSRI augmentation is unknown. Several SSRI antidepressants inhibit cytochrome P450 (CYP) enzymes, mainly CYP1A2 and CYP2D6 isozymes, which are metabolizers of antipsychotic drugs (Brosen 1998; Spina and de Leon 2007; Sproule et al. 1997). Therefore, combination of SSRI antidepressant with antipsychotic drug results frequently in higher plasma levels of the latter (Weigmann et al. 2001; Wetzel et al. 1998), which could potentially underlie the superior efficiency of the augmentation treatments. However, the improvement in negative symptomatology in schizophrenic patients under

Table 1 The use of SSRI–antipsychotic combinations in psychiatric disorders

Combination		Disorder	Literature
Antipsychotic	Antidepressant		
Olanzapine	Fluvoxamine	Schizophrenia	Chaichan (2004), Hiemke et al. (2002)
	Fluoxetine	Depression	Corey-Lisle et al. (2003), Corya et al. (2006), Dube et al. (2007), Shelton et al. (2005)
	Fluoxetine	Bipolar	Brown et al. (2006), Nierenberg (2007), Shi et al. (2004), Tohen et al. (2003), Amsterdam and Shults (2005), Keck et al. (2005), Owen (2006), Shelton (2003; 2006)
	SSRI[a]	OCD	Bystritsky et al. (2004), D'Amico et al. (2003), Francobandiera (2001), Marazziti et al. (2005), Shapira et al. (2004), Weiss et al. (1999)
Aripiprazole	SSRI[a]	Depression	Barbee et al. (2004), Goforth and Carroll (2007), Hellerstein (2004), Patkar et al. (2006), Rutherford et al. (2007), Simon and Nemeroff (2005), Worthington et al. (2005)
	SSRI[a]	Bipolar	Goforth and Carroll (2007), Hellerstein (2004), Kemp et al. (2007), Ketter et al. (2006), McElroy et al. (2007), Patkar et al. (2006), Rutherford et al. (2007), Sokolski (2007), Worthington et al. (2005)
Ziprasidone	SSRI[a]	Depression	Barbee et al. (2004), Papakostas et al. (2005)
Quetiapine	Lithium or valproate	Bipolar	Doree et al. (2007), Sokolski and Denson (2003)
	SSRI[a]	OCD	Bogan et al. (2005), Carey et al. (2005), Denys et al. (2004a), Sevincok and Topuz (2003)
Risperidone	Fluoxetine	Depression	O'Connor and Silver (1998), Ostroff and Nelson (1999)
	Fluvoxamine	Depression	Hirose and Ashby (2002)
	Paroxetine	Depression	O'Connor and Silver (1998)
	Citalopram	Depression	Rapaport et al. (2006)
	SSRI[a]	OCD	Bloch et al. (2006), Erzegovesi et al. (2005), Hollander et al. (2003), McDougle et al. (2000), Yoshimura et al. (2006)
Clozapine	Fluvoxamine	Schizophrenia	Lammers et al. (1999), Silver et al. (1995, 1996), Szegedi et al. (1999)
Haloperidol	Fluvoxamine	Schizophrenia	Silver et al. (2000), Silver and Nassar (1992), Silver and Shmugliakov (1998)

[a] Studies not focusing or specifying the particular SSRI drug used. *SSRI*, selective serotonin reuptake inhibitor, *OCD* obsessive-compulsive disorder

SSRI–haloperidol therapy did not correlate with the increase of antipsychotic levels in plasma (Avenoso et al. 1997; Hiemke et al. 2002; Yasui-Furukori et al. 2004). In addition, raising antipsychotic drug levels does not increase the efficacy of the drugs or the range of the responsive symptoms and may have adverse effects (Baldessarini et al. 1988; de Oliveira et al. 1995; Volavka et al. 2000). Moreover, in most of the combined antidepressant–antipsychotic treatments, the doses employed are lower than their therapeutic levels in monotherapy (Table 2). Finally, several effective augmentation treatments for schizophrenia used SSRI compounds (Poyurovsky et al. 2003; Weigmann et al. 2001; Wetzel et al. 1998) or other drugs (Goff et al. 2001; Goforth and Carroll 2007; Stoll and Haura 2000; Tsai et al. 2006) that have no pharmacokinetic interaction with antipsychotics. Thus, pharmacokinetic interactions cannot explain the clinical therapeutic efficacy of SSRI augmentation strategies for negative symptoms in schizophrenia.

The contribution of SSRI drugs as augmentation agents for negative symptoms appears to be distinct from "non-specific" antidepressant action. First, patients having prominent depressive symptoms were excluded from controlled clinical studies and the score of depression parameters for those individuals included in the study was low and did not change by the combined treatment. In addition, tricyclic antidepressants, which are equally effective antidepressants, do not improve negative symptoms in schizophrenic patients, though they can be useful when depression is associated with the disease (Siris 1993). Notably, SSRIs acting through serotonergic receptors, but not maprotiline which acts via noradrenergic receptors, are effective augmentative agents for negative symptoms (Silver and Shmugliakov 1998), suggesting the mechanism requires manipulation of the serotonergic system (Siris 1993). Paradoxically, clozapine and fluvoxamine–haloperidol combination produce a similar clinical effect despite their different pharmacology: clozapine, a "gold standard" in the treatment of negative symptoms in schizophrenia, is a serotonin (5HT) antagonist while the antidepressant fluvoxamine elevates 5HT receptor action. Furthermore, adding SSRI to clozapine may improve effectiveness (Silver et al. 1995, 1996). Thus, the mechanisms mediating the clinical effects are likely to be located downstream from the initial pharmacological effects of the drugs at the receptor/transporter levels.

In this review, we will discuss evidence examining some of the potential targets relevant to the mechanism of augmentative treatments (Fig. 1).

Candidate targets and mechanism of action of SSRI–antipsychotic combined treatment

Dopamine system

Cortical dopaminergic transmission

One of the most consistent animal findings on combined antipsychotic–SSRI treatments is the synergistic and

Table 2 Psychotropic drug dose in monotherapy and as augmentative agent

Drug	Dose (mg)/disease	
	Monotherapy	As augmentation agent
Olanzapine	15–20/schizophrenia (Bergemann et al. 2004; Nemeroff 1997)	6–12/depression (Corya et al. 2006; Shelton et al. 2005)
	11/schizophrenia daily dose (Simpson et al. 2004)	6–12/bipolar (Brown et al. 2006)
		10/OCD (D'Amico et al. 2003)
Risperidone	3–6/schizophrenia (Williams 2001)	0.5–1/depression (Hirose and Ashby 2002; O'Connor and Silver 1998; Ostroff and Nelson 1999)
		0.5–1/OCD (Erzegovesi et al. 2005; Yoshimura et al. 2006)
Quetiapine	300–800/schizophrenia (Citrome et al. 2005)	180/depression (Adson et al. 2004)
Ziprasidone	100–160/schizophrenia (Rasmussen 2006)	82/depression daily dose (Rasmussen 2006)
	80–160/schizophrenia (Kane et al. 2006)	
	130/schiz mdd (Simpson et al. 2004)	
Fluvoxamine	100–300/depression (Morishita and Arita 2003)	25–100/schizophrenia (Lammers et al. 1999; Silver et al. 1996, 2000; Szegedi et al. 1999)
	300/OCD (Yoshimura et al. 2006)	100/schizophrenia (Hiemke et al. 2002)
		50–100/schizophrenia (Chiu et al. 2004)
		100/schizophrenia (Szegedi et al. 1999)

OCD obsessive-compulsive disorder

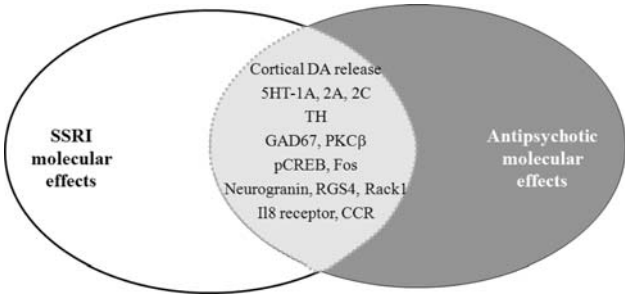

Fig. 1 Molecular targets potentially involved in the therapeutic synergistic effect of SSRI–antipsychotic treatment. The synergistic therapeutic effect of the combination of SSRI and antipsychotic drug is hypothesized to be reflected at the molecular level. The review discuses some targets that may be involved in the mechanism of action of this augmentation strategy

selective increase in frontal cortex extracellular concentrations of dopamine (DA) compared to each individual drug (Ago et al. 2005; Denys et al. 2004b; Dremencov et al. 2007; Gobert et al. 1997; Huang et al. 2006a; Koch et al. 2004; Yoshino et al. 2004; Zhang et al. 2000).

Several lines of evidence support the therapeutic relevance of enhanced DA release. Reduced monoaminergic activity in the frontal cortex is associated with negative symptoms of schizophrenia (Heinz et al. 1998; Weinberger and Berman 1996). Atypical antipsychotics such as clozapine, olanzapine and amperozide, which may improve cognitive and negative symptoms, enhance DA efflux in the frontal cortex while typical drugs, such as haloperidol, ineffective against negative symptoms do not induce DA release (Advokat 2005; Devoto et al. 2003; Ichikawa et al. 2002; Kuroki et al. 1999; Li et al. 1998; Moghaddam and Bunney 1990; Nomikos et al. 1994; Westerink et al. 2001; Yamamoto and Cooperman 1994; Youngren et al. 1999; Zhang et al. 2000). Furthermore, adding the monoamine oxidase inhibitor B (MAOI-B), selegiline, to antipsychotic may improve negative symptoms in schizophrenia patients (Bodkin et al. 2005).

The mechanism underlying the increase in cortical DA following SSRI–antipsychotic treatment is not clear but it is generally accepted that the 5HT system plays an important modulatory role. The effect of SSRI augmentation on DA neurotransmission appears to involve selective changes in activation of 5HT receptors throughout the brain rather than in cortical 5HT output (Ago et al. 2005; Huang et al. 2006a). Activation of 5HT-1A receptors (Ago et al. 2005; Gobert et al. 1997; Millan et al. 2000; Rollema et al. 2000; Yoshino et al. 2004) and antagonism at 5HT-2 heteroreceptors, mainly 5HT-2A and 5HT-2C, have been implicated in enhanced cortical DA/NE release (Bonaccorso et al. 2002; Cremers et al. 2007; Dremencov et al. 2007; Huang et al. 2006a; Liegeois et al. 2002; Marek et al. 2005; Pehek et al. 2006; Szabo and Blier 2002; Westerink et al. 2001). The findings of down-regulation of 5HT-2A following combined antipsychotic–fluvoxamine treatment in the peripheral mononuclear cells (PMC) of schizophrenia patients, parallel to the improvement in negative symptoms (Chertkow et al. 2007b) and the reduced expression in rat brain after administration of the atypical antipsychotic olanzapine (Huang et al. 2006b), support involvement of this receptor subtype in the mechanism of action of drugs enhancing cortical DA. Notably, 5HT acting on the widespread 5HT-2C receptors exerts a tonic inhibitory influence on DAergic neurotransmission, whereas it stimulates DAergic release, under facilitated conditions, through 5HT-2A receptors, located mainly in the cortex (Landen and Thase 2006).

An indirect serotonergic effect on cortical neurotransmission can occur via 5HT-2 receptors located in gamma-aminobutyric acid (GABA) and glutamate pathways, originating at the frontal cortex and projecting to the locus coeruleus (LC) and ventral tegmental area (VTA). These neuronal tracks, in turn, modulate both 5HT cell bodies at the LC or at the VTA and mesocortical DA neurons (Alex and Pehek 2007; Millan et al. 2000; Pehek et al. 2006), thus forming feedback/compensatory long-loop circuitry. Indeed, it was proposed that combined antipsychotic–antidepressant treatments potentiate DA/NE release in the frontal cortex through non-cortical serotonergic action (Ago et al. 2005; Seager et al. 2004, 2005).

Dopamine turnover and tyrosine hydroxylase (TH) modulation

Dopamine turnover is extensively altered by antipsychotic treatment. Combined haloperidol and fluvoxamine treatment, but not the individual drugs, reduced DA turnover in rat cerebellum and increased DA metabolites and TH protein level in the striatum (Chertkow et al. 2007a). Similarly, olanzapine combined with fluoxetine induced TH in rat LC (Ordway and Szebeni 2004) compared to the individual compounds. TH catalyzes the rate-limiting step in DA synthesis and may thereby affect the function of dopaminergic circuits, including DA neural firing (Melia et al. 1992; Mereu et al. 1983). Typical and atypical antipsychotic drugs show different, region specific effects on TH activity. Thus, clozapine and risperidone increased TH immunoreactivity in both medial prefrontal cortex (mPFC) and LC, while haloperidol caused a smaller increase in TH protein expression in the LC, and did not alter its levels in the mPFC (Verma et al. 2007).

Gamma-aminobutyric acid–glutamate systems

Postmortem studies demonstrated loss of specific GABAergic inhibitory neurons (Reynolds et al. 2001), reduction in the GABA synthesizing enzyme, glutamate decarboxylase

67 (GAD67) (Blum and Mann 2002; Hashimoto et al. 2008; Kalkman and Loetscher 2003; Volk et al. 2000) and compensatory upregulation of GABA-A receptor (Benes et al. 1996; Deng and Huang 2006) in brains of schizophrenia patients. In addition, hypofunction of the ionotropic glutamate *N*-methyl-D-aspartate (NMDA) receptor (Javitt 2006; Shim et al. 2008) may play an important role in the pathophysiology and treatment of negative symptoms and lead to inhibition of GABAergic interneurons (Konradi and Heckers 2003).

We recently reported that SSRI augmentation of antipsychotic decreased components involved in the modulation of GABA-A receptor activity, including GAD67 protein and protein kinase C (PKC) beta in the rat frontal cortex (Chertkow et al. 2006). In a pilot clinical study, we found reduced expression of receptor for activated C-kinase 1 (Rack1), involved in GABA-A receptor phosphorylation, in PMC of schizophrenia patients undergoing SSRI augmentation treatment (Chertkow et al. 2007b).

Antipsychotic drugs can modify GABA and glutamate system elements including GABA-A receptor, extracellular GABA levels, GAD67 expression, glutamate transporters (Schmitt et al. 2003), neuregulin-1 (which regulates the expression of NMDA and GABA-A alpha receptors) (Zhang et al. 2007) as well as ionotropic and metabotropic glutamate receptors (Fumagalli et al. 2008; Tarazi et al. 2003). Addition of SSRI to antipsychotic modifies these effects (Chertkow et al. 2006, 2007b). Interestingly, atypical antipsychotics differ from typical ones in the effect on GABA system including hippocampal and cortical GABA-A receptor density (Zink et al. 2004b), GABA transporter expression (Zink et al. 2004a) and GAD67 levels (Zink et al. 2004b). Possible mechanisms mediating drug-induced modification of GABA system include inhibition of DA innervations on the GABA and glutamate neurons, activation of PKC anchored to Rack1 (Feng et al. 2001), and increase in brain levels of allopregnanolone (Allo), a potent positive allosteric modulator of GABA at GABA-A receptor (Pinna et al. 2006).

There is clinical evidence linking GABA/glutamate agents with negative and cognitive symptoms in schizophrenia. Silver et al (2005) have demonstrated correlation between dehydroepiandrosterone (DHEAS) level and cognitive function in schizophrenia patients (Silver et al. 2005). Augmentation with DHEA (Strous 2005) or agonists at glycine site (Tsai et al. 2006; Heresco-Levy et al. 1999) has been reported to improve negative symptoms in schizophrenic patients maintained on antipsychotic drugs, excluding clozapine (Lane et al. 2006), which has glutamatergic activity (Advokat 2005; Spurney et al. 1999; Evins et al. 1997). These data suggest that clinical effectiveness may require specific and fine-tuning adjustments of glutamate system.

Transcription and neurotrophic factors in SSRI–antipsychotic combined treatment

Transcription and neurotrophic factors have multiple effects on intracellular signaling pathways and they are key factors in the modulation of neuronal plasticity and synaptic activity (Colombo 2004; Nikitin 2007; Tischmeyer and Grimm 1999; Murer et al. 1999; Wetmore et al. 1990; Linnarsson et al. 2000; Pezet et al. 2002; Pillai 2008; Roberts et al. 2006; Spedding and Gressens 2008; Dono 2003; Otto and Unsicker 1990). Preliminary data suggest that they may have a role in the mechanism of action of the combined treatment.

Subchronic (7 days) fluoxetine–olanzapine treatment suppressed the induction of phospho-cyclic adenosine monophosphate response element-binding protein (pCREB) and the transcription factor Fos in rat frontal cortex and hippocampus (Horowitz et al. 2003), while a single injection had no effect in the hippocampus and striatum (Maragnoli et al. 2004). Studies in brains of naive rats reported modified levels of Fos alone in its complex with Jun (AP-1 complex) following chronic antipsychotic treatment (Cochran et al. 2002; Cohen and Wan 1996; Kontkanen et al. 2002). Moreover, it was suggested that typical and atypical drugs have differential effects on Fos expression (Deutch and Duman 1996; Semba et al. 1999; Wan et al. 1995; Werme et al. 2000) and CREB phosphorylation (Pozzi et al. 2003), which may lead to different neural activity and therapeutic outcome. In addition, postmortem studies in schizophrenia patients reported changes in pCREB (Kyosseva et al. 2000) and Fos (Kyosseva 2004) levels in the thalamus and cerebellar vermis.

The neurotrophic factors, brain-derived neurotrophic factor (BDNF) and fibroblast growth factor (FGF-2) have been implicated in the pathophysiology and the treatment response of schizophrenia (Buckley et al. 2007; Fumagalli et al. 2004; Huang and Lee 2006; Lu and Martinowich 2008; Pillai 2008; Tan et al. 2005). Chronic administration of quetiapine combined with venlafaxine in rats prevented the decrease in hippocampal cell proliferation and BDNF expression induced by chronic restrain stress in a synergistic and dose-dependent manner (Xu et al. 2006). Repeated treatment with the fluoxetine–olanzapine combination induced FGF-2 levels in the striatum and the hippocampus, in addition to the prefrontal cortex in which FGF-2 was upregulated after a single dose only (Maragnoli et al. 2004). In addition, there are indications for distinct effects of typical and atypical antipsychotic drugs on BDNF and FGF-2 (Balu et al. 2008; Chlan-Fourney et al. 2002; Parikh et al. 2004; Pillai et al. 2006; Riva et al. 1999). Future work needs to clarify the significance of these alterations and whether they contribute to the specific effects of the combined drug action or represent a general neuroleptic action.

Calcium signaling pathway

It has been suggested that dysfunction of calcium (Ca) signaling may explain many of the morphological and functional alterations observed in schizophrenia (Lidow 2003). Binding of glutamate to the NMDA receptor, implicated in schizophrenia (Tsai and Coyle 2002), causes an influx of Ca, which triggers the phosphorylation of the postsynaptic brain-specific protein neurogranin by PKC (Rodriguez-Sanchez et al. 1997) and the release of calmodulin from neurogranin (Chakravarthy et al. 1999). The "free" calmodulin complex with Ca and activates Ca^{2+}/calmodulin-dependent kinase II (CaMKII) that plays an important role in synaptic plasticity, learning and memory (Huang et al. 2004; Pak et al. 2000).

Several components of the Ca signaling system have been reported to be abnormal in schizophrenia. Recent studies indicted that neurogranin gene is associated with schizophrenia (Ruano et al. 2008) and that neurogranin and calmodulin protein expression are altered in the prefrontal cortex of schizophrenic patients (Broadbelt and Jones 2008). Loss of neurogranin may lead to changes in long-term potentiation and spatial learning (Pak et al. 2000). There is also evidence that CaMKII is altered in schizophrenia (Novak et al. 2006) and following haloperidol treatment (Fumagalli et al. 2008). Regulators of G-protein signaling (RGS) proteins, RGS4 and RGS2, modulate NMDA receptor activity through serotonergic and noradrenergic receptors (Gu et al. 2007; Liu et al. 2006) and thus affect intracellular Ca levels. Several studies indicate that RGS4, RGS2, RGS5, RGS9 and RGS10 are involved in the pathophysiology of schizophrenia and its drug treatments (Campbell et al. 2008; Erdely et al. 2006; Fatemi et al. 2006; Hishimoto et al. 2004; Mirnics et al. 2001; Seeman et al. 2007). PKCβII is involved in calcium signaling through its interaction with the intracellular scaffold protein RACK1 (Patterson et al. 2004). Interestingly, we have found changes in PKCβII levels in PFC of naive rats following chronic fluvoxamine–haloperidol treatment (Chertkow et al. 2006). There is preliminary clinical evidence that combined SSRI–antipsychotic treatment may have selective effects on components of the calcium cascade (neurogranin, RGS family and Rack1) in PMC from schizophrenia patients (Chertkow et al. 2007b).

Cytokines

Growing evidence demonstrates that the nervous system interacts with the brain and peripheral immune and endocrine systems through neurotransmitters, hormones and cytokines (Kronfol and Remick 2000). In line with this notion, data from the recent years indicated that schizophrenia pathology might involve impairments in cytokine profile, including balance in helper T cells (Th1/Th2), and in the levels of interleukin (IL)-2, IL-6, IL-8 and IL-10 (Potvin et al. 2008; Schwartz and Silver 2000; Zhang et al. 2005). Specifically, it was suggested that elevated cortisol levels are associated with negative symptoms and high IL-2 concentration with positive symptoms (Zhang et al. 2005). The effects of antipsychotic treatment on cytokine network have been previously examined and reviewed (Drzyzga et al. 2006; Pollmacher et al. 1996; Zhang et al. 2005). The most robust data focus on tumor necrosis factor α (TNF-α), IL-2, IL-10 and IL-6 (Drzyzga et al. 2006), but it is as yet unclear whether a characteristic cytokine profile is associated with therapeutic response (Drzyzga et al. 2006).

Clinical support for involvement of cytokines in mechanism of SSRI augmentation comes from a study showing time-dependent changes in the expression levels of IL-8 receptor and chemokine (C–C motif) receptor 1 (CCR1) in PMC of schizophrenia patients following addition of fluvoxamine to ongoing antipsychotic treatment (Chertkow et al. 2007b). Importantly, the molecular changes paralleled reduction in negative symptoms (Chertkow et al. 2007b). IL-8, essential for the directional migration of leukocytes, is increased in the serum of unmedicated chronic schizophrenia patients (Erbagci et al. 2001; Maes et al. 2002; Zhang et al. 2002). Thus, it is plausible that augmentation therapy of SSRI and antipsychotic drug acts to equilibrate the pathological increase in IL-8 receptor concentration.

Summary and future perspective

Negative symptoms in schizophrenia, like other "treatment resistant" symptoms of psychiatric illnesses, continue to be a therapeutic challenge. New molecular targets are needed to develop novel and more effective pharmacotherapeutic compounds. Given the complexity of the symptoms, it is unlikely that "single-action" drugs, given alone, will be effective and a multifunctional approach, as in augmentation treatment, may be needed. The studies reviewed here encourage the view that combined SSRI–antipsychotic treatment results in unique molecular changes in the brain which differ from those of the individual drugs (Fig. 1). We have highlighted some plausible molecular meeting points for actions of pharmacologically distinct treatments which may underlie their convergent clinical effects. These are localized anatomically, and involve systems at various cellular levels, downstream from the initial impact of the drugs on membrane receptors or transporters (Fig. 2). They modify widespread pathways and inter-cellular processes such as, rate of neurotransmission, connectivity, plasticity and proliferation.

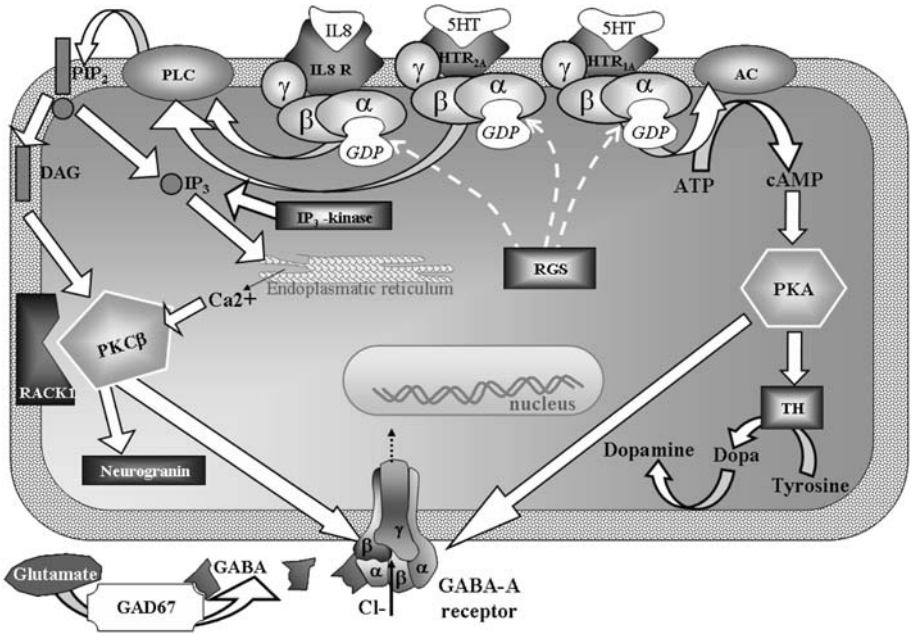

Fig. 2 A schematic illustration of some signaling pathways potentially involve in the synergistic therapeutic effect of SSRI–antipsychotic combination. The diagram depict the connection between some of the molecular targets discuss in the text, which may underlie the synergistic therapeutic effect of SSRI–antipsychotic combination. Intracellular signaling cascades and neural action are modified through G-protein coupled receptors activated or inhibited by natural ligands (5HT, IL-8, etc.) or medications. Enhanced cortical DA/NE release following SSRI–antipsychotic combination involves the action on 5HT-1A and 5HT-2 receptors and the input of tyrosine hydroxylase (TH), catalyzing DA synthesis. Receptor activity is also modulated intracellularly by RGS family proteins. Conductance of a Cl^- through GABA-A receptor channel is regulated by PKCβ acting on β3 subunit and by the natural ligand GABA, whose level is modified by GAD67. GABA-A activity is also modulated by negative coupling (for example with D2-family receptor antagonists) with subtypes of Gi and/or Go, and the consequent un-inhibition of adenylyl cyclase (AC) and phospholipase C (PLC). Higher levels of cAMP enhance cAMP-dependent protein kinase activity (PKA) and GABA-A phosphorylation. In addition, activation of the cAMP pathway increases catecholamine synthesis via increases phosphorylation of TH. The relation of Rack1 and neurogranin, which are discussed in the text, is also depicted in this diagram. *PKC* protein kinase C, *PKA* protein kinase A, PIP_2 phosphatidylinositol-4,5-bisphosphate, *DAG* diacylglycerol, IP_3 inositol trisphosphate, *5HT* serotonin, *RGS* regulator of G-proteins, *GAD* glutamate decarboxylase

In current psychiatric practice, a decision to add a second drug is usually made after monotherapy fails to achieve a satisfactory response (Ostroff and Nelson 1999; Rutherford et al. 2007; Silver et al. 1996; Tani et al. 2004; Zink 2005). This imposes both an interval between drug administration and a treatment-specific intake order (i.e. in schizophrenia antipsychotics are given first, while in depression and OCD, SSRIs initiate the treatment). It is unclear if and how the interval between the onsets of administration of the two drugs and their order influences response. For example, in depression co-administration of risperidone and fluvoxamine, from the beginning of therapy is efficacious (Hirose and Ashby 2002), while in treatment of negative symptoms augmentation typically begins several weeks into antipsychotic treatment. These parameters have implications for both the understanding of the mechanism of combined antipsychotic–antidepressant therapy and for deciding on the appropriate treatment regimen.

Clearly, the available data are limited, and much research is needed to identify and validate the molecular targets of SSRI–antipsychotic and other augmentation treatments. Conceptually, the method of isolating molecular effects of pharmacologically distinct but clinically convergent drugs provides a useful "window" for understanding of the mechanisms of multifunctional treatments and development of new more effective drugs for the treatment of schizophrenia.

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