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Towards better non-selectivity: the role of 5-HT$_7$ receptors in therapeutic efficacy of a second-generation antipsychotic – lurasidone

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Summary

Effectiveness of currently available antipsychotic medications is far from satisfactory with many patients showing incomplete therapeutic response even after many trials with different antipsychotic drugs. Hence, there is an ongoing interest in searching for pharmacological mechanisms, which could potentiate therapeutic response to antipsychotic drugs and/or reduce its typical side effects. The primary aim of this mini-review is to summarize available evidence supporting the role of serotonin receptors, especially 5-HT$_7$ receptors, in therapeutic effects of a second-generation antipsychotic drug, lurasidone.

Key words: lurasidone, schizophrenia, bipolar depression, serotonin receptors, 5-HT$_7$ receptors

Introduction

Response to currently available antipsychotic medications is far from satisfactory with many psychiatric patients showing incomplete therapeutic response even after many trials with different drugs administered at adequate doses [1, 2]. Hence, there is an ongoing interest on the side of industry and academia in searching for pharmacological mechanisms, which could potentiate therapeutic response to antipsychotic drugs and/or reduce its typical side effects, including metabolic abnormalities, QTc prolongation, cognitive and motor dysfunctions [3–5].

The primary aim of this mini-review is to summarize available evidence supporting the role of serotonin 5-HT_7 receptors in therapeutic effects of new antipsychotic drugs with special emphasis given to a recently approved in some countries second-generation antipsychotic drug, lurasidone. The mini-review is focused on lurasidone as this antipsychotic has been recently approved for the treatment of schizophrenia and bipolar depression and its widespread use in psychiatric patients can be expected.

Serotonin 5-HT_7 receptors in the nervous system

Serotonin 5-HT_7 receptors occur in the central and peripheral nervous system. In the brain, the 5-HT_7 receptors were detected predominantly in the frontal cortex, thalamus, hypothalamus, and hippocampus [6, 7]. The distribution of 5-HT_7 receptors in the central nervous system supports its role in the regulation of cognitive processes, mood states, pain, circadian rhythms, and sleep [8, 9]. In line with this assumption, both genetic inactivation and pharmacological blockade of the 5-HT_7 receptor led to anti-depressant-like effects in animal models of depressive symptomatology [9, 10].

The localization and function of 5-HT_7 receptors prompted several research groups to develop molecules with high affinity at the 5-HT_7 receptors targeting various neuropsychiatric disorders, including, among others, schizophrenia, cognitive dysfunctions and depression. Recent discoveries that a potent atypical antipsychotic drug with antidepressant properties, amisulpride, apart from well-know antagonism at dopamine D_2 receptors, has high affinity at 5-HT_7 receptors [11] gave further support to the concept that 5-HT_7 and D_2 antagonists, e.g. lurasidone, may provide some benefits in the therapy of schizophrenia and affective disorders [12].

Basic pharmacological characteristics of lurasidone

Lurasidone (formerly known as SM-13496) is an azapirone derivative with antipsychotic and antidepressant properties confirmed in preclinical models and randomized clinical trials [5, 13]. In vitro studies revealed that lurasidone has potent binding affinity for dopamine D_2, 5-HT_{2A}, 5-HT_7, 5-HT_{1A}, and noradrenaline $alpha_{2C}$ receptors. Affinity for several other dopamine, serotonin, and noradrenaline receptors was weak, whereas affinity for histamine H_1 and muscarinic acetylcholine receptors was negligible. In vitro functional assays showed that the drug acts as an antagonist at dopamine D_2 and serotonin 5-HT_{2A} and 5-HT_7 receptors and as a partial agonist at the serotonin 5-HT_{1A} receptor [12–14].

Studies with animal models predictive of antipsychotic efficacy have indicated that lurasidone can exert potent and dose-dependent antipsychotic-like effects, the observation consistent with its high affinity to dopamine D_2 receptors [14, 15]. In agreement with its affinity at serotonin receptors, lurasidone showed antidepressant-like and anxiolytic-like effects in animal models of anxiety disorders and depression. In line

with its high affinity to 5-HT$_{1A}$, 5-HT$_{2A}$, and 5-HT$_7$ receptors, lurasidone had only weak extrapyramidal effects in animal models predictive of drug-induced extrapyramidal side effects [14, 15].

Effects of lurasidone in animal models of depressive symptomatology: possible involvement of 5-HT$_7$ receptors

Low doses of lurasidone exerted antidepressant-like effects in the classic test used for predicting antidepressant efficacy of psychoactive drugs, i.e. in the Porsolt forced swim test in rats [15]. In mice, lurasidone decreased immobility, i.e. produced antidepressant-like effects, both in the tail suspension test and the forced swim test [16]. The role of 5-HT$_7$ receptors in antidepressant-like effects of lurasidone has been addressed in experiments with mice lacking functional 5-HT$_7$ receptors. The antidepressant-like effect of lurasidone required functional 5-HT$_7$ receptors as it was absent in mice lacking the functional 5-HT$_7$ receptor gene [16].

In agreement with the above findings, there is a large body of evidence that 5-HT$_7$ receptors antagonists can exert antidepressant-like effects in animal models predictive of antidepressant efficacy. Compounds acting as 5-HT$_7$ receptors antagonists were active in the Porsolt forced swim test and the tail suspension test [10, 17]. In line with the above, inactivation of the 5-HT$_7$ receptor gene led to antidepressant-like phenotype, that is to reduced immobility in a challenging situation, in mice [9].

Ineffective doses of 5-HT$_7$ antagonists and clinically active antidepressant drugs induced a synergistic antidepressant-like effect in the animal models. For example, a concurrent administration of subthreshold doses of citalopram and a 5-HT$_7$ antagonist, SB 269970 reduced immobility in the tail suspension test in mice [9, 18]. Interestingly, the behavioural observations were supported by neurochemical studies showing that a low ineffective dose of citalopram and a low ineffective dose of the 5-HT$_7$ antagonist produced synergistic serotonergic effects, i.e. increased serotonin levels, in the frontal cortex [18]. The synergistic interaction does not depend on pharmacological properties of an antidepressant. Ineffective doses of desipramine, imipramine, and moclobemid also exerted antidepressive-like effects when given in combination with a low dose of 5-HT$_7$ receptor antagonist [10].

There is some indirect clinical evidence supporting the role of 5-HT$_7$ receptors in antidepressant properties of clinically effective psychotropic medications. A second-generation antipsychotic, amisulpride is also an antidepressant active in monotherapy and as an augmentation of response to SSRIs [19, 20]. Recently, it has been reported that amisulpride is a potent 5-HT$_7$ receptor antagonist and that its antidepressant-like properties in animal models depend on intact 5-HT$_7$ receptors. As in the case of lurasidone, amisulpride did not reduce immobility in 5-HT$_7$ knock-out (5-HT$_7^{-/-}$) mice, i.e. in animals without functional 5-HT$_7$ receptors in the brain [11].

One should not neglect the role of other serotonin receptors (e.g. 5-HT_{1A}) in the antidepressant effects of lurasidone. In fact, it has been suggested that interactions between 5-HT_7 and 5-HT_{1A} receptors may be of crucial importance for antidepressant effects of new medications [2, 21]. It is worthy to note that a new multimodal antidepressant, vortioxetine is a potent antagonist at 5-HT_7 receptors and agonist at 5-HT_{1A}. Thus, although belonging to different classes of psychotropic medications, lurasidone and vortioxetine share at least two important pharmacological mechanisms thought to be directly involved in their therapeutic profile [1, 2, 22, 23].

In conclusion, the preclinical studies strongly support the role of 5-HT_7 receptors in antidepressant effects of lurasidone. Blockade of 5-HT_7 receptors may be a neurobiological substrate of the antidepressant efficacy of lurasidone both in monotherapy and in combination with antidepressant drugs and mood stabilizers [2, 10, 17, 24].

Effects of lurasidone in animal models of learning and memory: focus on 5-HT_7 receptors

Cognitive impairment is one of the major symptoms of various psychiatric disorders, including depression and schizophrenia [24–26]. Cognitive deficits in schizophrenia and depression are considered largely due to dysfunctions in the prefrontal cortex. Hence, there is an ongoing interest in developing psychotropic medications that, apart from basic antidepressant or antipsychotic properties, could reverse prefrontal hypofunction and its cognitive correlates [27, 28].

Lurasidone was tested in many animal models of learning and memory. The drug showed a unique profile in the rat passive avoidance test, a well-established animal model based on aversive Pavlovian conditioning. In a series of experiments described by Ishiyama et al. [29] olanzapine, clozapine, quetiapine, risperidone, and aripiprazole suppressed passive avoidance conditioning when given alone before a conditioning session in which foot shocks were paired with a distinct experimental environment. Lurasidone was the only antipsychotic medication, which did not inhibit the acquisition of passive avoidance conditioning when given alone. In addition, lurasidone reversed cognitive deficits induced by an NMDA receptor antagonist, dizocilpine (MK-801) [29]. The latter effect was mimicked by clozapine, risperidone, and quetiapine but not by haloperidol, olanzapine and aripiprazole. MK-801 is a psychotomimetic drug thought to exert schizophrenia-like behavioural and cognitive states in animals and humans. Notably, in the study by Ishiyama et al. [29] lurasidone was equally potent in reversing MK-801-induced cognitive deficits when given before and after the conditioning session. The latter finding may indicate that lurasidone not only prevents MK-801-induced cognitive impairment but also improves memory already disrupted by the psychotomimetic agent.

Horisawa et al. [30] addressed receptor mechanism involved in lurasidone-induced reversal of memory impairment induced by MK-801. Lurasidone reversed

MK-801-induced deficits in Pavlovian conditioning and in the Morris water maze, a widely-used model of spatial memory. The authors reported that selective antagonists of 5-HT$_7$ (SB-656104-A) and 5-HT$_{1A}$ receptors (WAY-100635) mimicked the effects of lurasidone on memory impairment induced by MK-801 in the passive avoidance test. Only the 5-HT$_7$ receptor antagonist, SB-656104-A mimicked the effect of lurasidone in the model of spatial memory. The above findings suggest that the pharmacological interaction with 5-HT$_7$ receptors, and to some extend with 5-HT$_{1A}$ receptors, may be involved in beneficial effects exerted by lurasidone in animal models of cognitive deficits induced by the psychotomimetic NMDA receptor antagonist [30].

Phencyclidine (PCP) is another NMDA antagonist with psychotomimetic properties in animal and human subjects. Chronic PCP administration leads to a variety of memory and emotional deficits similar to cognitive and negative symptoms of schizophrenia. Of particular interest are persistent deficits in working memory produced by chronic PCP pre-treatment [25, 31]. Lurasidone reversed working memory deficits induced by chronic PCP administration in the rat novel object recognition test. The effect of lurasidone was mimicked by a 5-HT$_7$ receptor antagonist, SB-269970, which also dose-dependently reversed PCP-induced object recognition deficits. A subeffective dose of the 5-HT$_7$ antagonist, given in combination with a subeffective dose of lurasidone, reversed PCP-induced cognitive impairment. In line with the above, the ability of lurasidone to reverse PCP-induced working memory deficits was blocked by a relatively selective 5-HT$_7$ receptor agonist, AS-19. In line with the concept linking procognitive effects of lurasidone with 5-HT$_7$ receptors, similar results were obtained for another second-generation antipsychotic drug with high affinity to 5-HT$_7$ receptor, amisulpride [31]. One should be aware that 5-HT$_7$ receptors may be involved in procognitive effects of vortioxetine, the antidepressant medication blocking the 5-HT$_7$ receptor [23].

The beneficial effect of lurasidone on cognitive processes has also been documented in monkeys. In the study on executive function in common marmosets, haloperidol, olanzapine and risperidone decreased correct performance. Lurasidone dose-dependently increased marmosets' success rates in difficult trials of the object retrieval task [32].

Clinical efficacy and safety of lurasidone

Schizophrenia

Schizophrenia is a chronic and "debilitating" psychiatric disorder generating high economic and social costs for both the patient and societies. Although the clinical course of schizophrenia is highly variable and difficult to predict with currently available assessment tools, it has been shown repeatedly that a substantial proportion of patients cannot achieve functional remission even after many trials with different second-generation antipsychotics [1, 22, 33].

Lurasidone is a relatively new second-generation antipsychotic approved for the treatment of schizophrenia (the US and Europe) and bipolar depression (the US). The recommended daily doses range from 40 mg to 160 mg, administered once daily with food. The starting dose is 40 mg and initial dose titration is typically not needed [13, 34, 35]. The efficacy of lurasidone in the treatment of acute episodes of schizophrenia was confirmed in several randomized controlled trials (for review [3, 22]). The available evidence suggests that lurasidone is well tolerated. In line with its low affinity at the histamine H_1 and muscarinic receptors, the drug induced minimal weight gain and showed benign metabolic profile. In general, no clinically-meaningful changes in lipids, glucose, and corrected QT interval (QTc) were found in those trials. The most common side effects were somnolence, akathisia, nausea, and parkinsonism. However, one should stress that the lurasidone's potential to induce parkinsonian symptoms was low [1, 22, 33].

Harvey et al. [28] examined effects of lurasidone on cognitive performance in patients with schizophrenia recruited to a 6-week double-blind study and randomized to lurasidone (80–160 mg), quetiapine XR (200–600 mg) and placebo. Cognitive performance was evaluated with the Cog-State computerized cognitive battery. For the evaluable sample, lurasidone 160 mg was superior to both placebo and quetiapine on the neurocognitive composite, while lurasidone 80 mg, quetiapine XR, and placebo did not differ. Patients meeting prespecified criteria entered a 6-month, double-blind extension study with lurasidone (40–160 mg) and quetiapine XR (200–800 mg). In the extension study, analysis of the full sample showed significantly better cognitive performance in the lurasidone group compared to the quetiapine XR group after both 3 and 6 months [28]. Although the report of Harvey et al. [28] needs replication, the findings provide some support to the concept linking the pharmacological profile of lurasidone to beneficial effects on cognitive dysfunctions associated with schizophrenia. Interestingly, in a recent preclinical study comparing several second-generation antipsychotics (aripiprazole, clozapine, lurasidone, olanzapine, sertindole) with haloperidol, lurasidone was the only antipsychotic medication free of debilitating effects on social exploration and social recognition in the social recognition test [36]. Further studies are needed to evaluate effects of lurasidone on different domains of social cognition in schizophrenia patients.

Bipolar depression

Bipolar disorder is another recurrent, debilitating psychiatric disorder generating high economic and social costs for both patients and societies. The course of bipolar disorder is highly variable with many patients suffering from multiple episodes of mania and depression leading to social incapacity in about 30% of individuals [12, 24]. Lurasidone was recently approved by the U.S. FDA for the treatment of bipolar

depression. The drug can be used as monotherapy or in combination with lithium or valproate [12, 37].

Two recently published clinical trials supported the above approval. Loebel et al. [38] have studied efficacy and safety of lurasidone monotherapy in the treatment of major depression in the course of bipolar I disorder in a randomized, double-blind, placebo-controlled phase III study. Monotherapy with lurasidone (20–120 mg/day) significantly reduced depressive symptoms measured by the Montgomery-Åsberg Depression Rating Scale (MADRS) in patients with bipolar I depression. In addition, lurasidone-treated patients experienced significant improvements, as compared to placebo-treated individuals, in anxiety symptoms and in patient-oriented measures of quality of life (QoL) and functional impairment. The authors concluded that lurasidone was generally well-tolerated as discontinuation rates due to adverse events were similar in the 20–60 mg/day, 80–120 mg/day, and placebo groups (6.6%, 5.9%, and 6.5%, respectively). Minimal changes in measures of glycemic control, lipids, and weights were found in lurasidone-treated patients. The most frequent adverse events observed in the lurasidone-treated groups were nausea, headache, akathisia, and somnolence.

In another study, Loebel et al. [39] evaluated the efficacy and safety of lurasidone as add-on therapy to lithium or valproate in bipolar I depression patients. Lurasidone treatment for six weeks significantly reduced the severity of depressive symptoms, assessed by the MADRS, as compared to the placebo group. Lurasidone produced also a significant improvement in anxiety symptoms and in patient-oriented measures of QoL and functional impairment. Discontinuation rates due to adverse events were closely similar to that reported for lurasidone monotherapy (6% and 7.9% in the lurasidone and placebo groups, respectively) suggesting a reasonable tolerance for the lurasidone-lithium and lurasidone-valproate combinations [38]. Side effects most frequently reported for the antipsychotic were nausea, somnolence, tremor, akathisia, and insomnia. As in the previous studies, relatively mild changes in lipids, glycemic control, and body weight were found in lurasidone-treated patients [39, 40].

The above observations are supported by a recent report by Nasrallah et al. [40]. The authors pooled data on depressive symptomatology measured by the MADRS from four double-blind, placebo-controlled, six-week registration studies of lurasidone (40–160 mg/d) in adult subjects with an acute exacerbation of schizophrenia. The post hoc analysis revealed that lurasidone produced a significant improvement in depressive symptomatology as compared to placebo. Notably, the antidepressant properties of lurasidone in schizophrenia patients were independent of baseline severity of depressive symptomatology (MADRS score of > 12, > 14, > 16, > 18 points) [40].

Conclusions

Lurasidone is a relatively new antipsychotic drug with a unique pharmacological profile combining blocking of dopamine D_2, serotonin 5-HT_{2A} and 5-HT_7 receptors with partial agonism to serotonin 5-HT_{1A} receptor [4, 41] – in the absence of a clear affinity for histamine H_1 and muscarinic cholinergic receptors.

The increasing body of preclinical evidence suggests the critical role of 5-HT_7 receptors in procognitive and antidepressant effects of psychoactive medications, including an antidepressant, vortioxetine and second-generation antipsychotics, amisulpride and lurasidone [9, 11, 23, 30]. Preliminary evidence gathered in the course of phase II and phase III trials with lurasidone tend to confirm the above assumption but the role of other serotonin receptors in the clinical profile of lurasidone cannot be neglected [2, 12, 38].

Although lurasidone seems to be an interesting, new tool in the therapy of schizophrenia and bipolar I depression, more experimental and clinical data are needed to fully justify the above conclusions.

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