Review

Pharmacological Mechanisms Underlying the Association of Antipsychotics with Metabolic Disorders

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ABSTRACT: Obesity and metabolic syndrome in association with an increased risk of cardiovascular disease and type II diabetes are significant problems that contribute to lower life expectancy of patients with schizophrenia. Understanding the pharmacological mechanisms of the current antipsychotic treatment is clearly the key to the improvement of pharmacotherapy, to avoid or to mitigate the metabolic adverse effects.

***KEY WORDS**: antipsychotic, pharmacological mechanisms, metabolic disorders.*

Introduction

Schizophrenia affects around 0.3-0.7% of the population at some point in life [1] or 24 million people worldwide in 2011 [2]. This is 1.4 times more common in men, with a peak occurrence of disease in men 20-28 years and women 26-32 years [3]. These worrying figures adding that life expectancy of people with schizophrenia is 12 to 15 years less, the result of physical health problems and increased frequency of suicide (about 5%) [1]. Prevention is difficult because there are no reliable indicators to predict the later development of the disease [4].

While there is some evidence that early intervention on people with a psychotic episode may improve long-term outcomes [5], trying to prevent schizophrenia in the prodromal phase has uncertain benefits, and in 2009 such tests were not recommended [6].

Thus prevention is difficult and therefore the emergence and the evolution of the disease is inevitable, researchers are trying to understand what is happening at the genetic and neurological level to develop appropriate therapies.

The development of new antipsychotic drugs has improved the lives of millions of patients with schizophrenia. However, despite the recognized importance and the extensive use of these drugs, it could be argued that there was no fundamental breakthrough since the first antipsychotic, chlorpromazine, in the way that works, all existing drugs requiring the dopaminergic D2 receptor antagonism. [7]

The neuroimaging studies that determine the degree of dopamine D2 receptor occupancy have demonstrated that the antagonism of these receptors is an essential feature for antipsychotic efficiency.

The side effects associated with the typical antipsychotics are usually neurological and include extra pyramidal symptoms and tardive dyskinesia. [8]

Nowadays all the guidelines, the recommendations and the assistance rules recommend that the first-line treatment of schizophrenia, atypical antipsychotics (except clozapine which, because of the risk of agranulocytosis/granulocytopenia posed, is an second line antipsychotic, suited only in cases resistant to the treatment).

Although the antipsychotics have improved the prospects of many patients with schizophrenia and are widely used, their effectiveness remains limited.

The negative symptoms (social withdrawal, apathy, poverty of speech and anhedonia) and cognitive impairment respond poorly to treatment, these being the most important factors in obtaining therapeutic results and allowing patients to return to society.

The initial enthusiasm for atypical antipsychotics, with a lower incidence of extra pyramidal symptoms, was tempered by the association with metabolic disorders. Weight gain is the most recognized metabolic effect, although this varies significantly among atypical antipsychotics: clozapine and olanzapine had the highest risk, quetiapine and risperidone moderate risk, aripiprazole, amisulpride and

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ziprasidone the lowest risk, with a negative impact on the adherence to treatment and the quality of life.

Characteristics of the antipsychotic action - brain receptors

The preclinical research of the antipsychotics faces serious difficulties that are not generally found in drugs with somatic effects. It is primarily about the lack of experimental models. It is very difficult to say whether or not animals can present mental illnesses similar to those in humans. Besides, even in humans, at least some psychopathological manifestations we know only as they are reported by the patient, having virtually no paraclinical methods available to objectify these phenomena. This meant that the antipsychotic effect is found almost incidentally, and the knowledge of the action mechanism is possible through a process that is rather associative than a cause-effect type.

The typical or atypical antipsychotics are characterized from the pharmacological point of view through a multireceptor affinity, basically interacting with about 16-18 receptors among which we could mention dopamine, serotonin, cholinergic-muscarinic, adrenergic, histamine (including their subtypes). The antipsychotics are inhomogeneous in terms of structure, but also from the point of view of the pharmacological properties and not least from the therapeutic properties [9]. The affinity order, decreasing for the D2 receptors (except aripiprazole that is agonist/antagonist) is the following:
risperidone>ziprasidone>olanzapine>clozapine> quetiapine.

For example, clozapine has an affinity for D1 and D4 receptors greater than that for the D2 receptor. Unlike the typical antipsychotics, the atypical ones, except aripiprazole and amisulpirid, have much higher affinity as antagonists for 5HT2A receptor than for the D2 receptors. The atypical antipsychotics are antagonists for 5HT2C receptors and partial agonists for 5HT1A receptors. We retain, with consequences especially in terms of adverse effects, the antihistamines effects, α1and α2 adrenergic blockers and antimuscarinic (M1). [8], [10]

Mechanisms of weight gain

The presence of obesity in patients with schizophrenia is two times higher than in the general population [11], and the metabolic syndrome is reported with a prevalence of 40% in chronic schizophrenia [12], [13]. The metabolic disorders manifested by rapid weight gain lead to obesity along with dyslipidemia and glucose intolerance and may develop type 2 diabetes. Another result may be cardiovascular diseases that contribute to a drop in life expectancy and an increased incidence of mortality among people with psychiatric illnesses. It is difficult to determine whether the prevalence of metabolic disorders is increased in this population independent of antipsychotic treatment or a side effect of medication. Factors associated with antipsychotics that induce weight gain include demographic factors (age, gender), other diseases, past and current medications, dosage and duration of treatment with antipsychotic, treatment response, the first episode of psychosis, genetic predisposition, stress, smoking, diet and physical activity [14]. The elevated cortisol concentrations-characteristic for the acute periods with psychomotor agitation and generalized anxiety-can explain insulin resistance and frequent periods of persistent hyperglycaemia that not occurs in chronic patients stabilized under the effect of antipsychotic medication therapy that is not consistently associated with hypercortizolemia periods. The comparison to the body mass index distribution in patients with schizophrenia compared to the general population indicates that people with schizophrenia are more likely to become overweight or obese. Weight gain associated with antipsychotic medications is considered co-occurring phenomena rather than the results of a safe physiopathology. The effects of weight gain caused by antipsychotic may be at least partially mediated by the hypothalamus. An important neuropeptide with a weight gain potential is Brain Derived Neurotrophic Factor (BDNF) which is involved in a variety of neuronal processes through its effects on synaptic plasticity, neuronal growth and differentiation, with an anorexigenic endocrine activity. BDNF signalling disruption may cause increased food intake and obesity [15]. Since the first meta-analysis [16], studies have consistently shown that clozapine and olanzapine are associated with the greatest increase in weight, with intermediate effects quetiapine, risperidone and chlorpromazine, and minimal changes to the weight produced by haloperidol, ziprasidone and aripripazol.

The disruption of the hypothalamic control

The growth of plasmatic leptin in patients receiving antipsychotic for 10 weeks [17], for one year [18] or for a longer period [19], [20], and the antipsychotic therapy initiation show a response produced at the antipsychotic medication and not a normal response to the increasing of patient fat deposits, not realizing an anorexigen effect. The broadcast signal of the anorexigen mechanism to the hypothalamus is disrupted by the antipsychotic medication. Although antipsychotics have no effect on hypothalamic regions involved in the control of food intake, we find that olanzapine increases expression of neuropeptide Y (NPY) in the arcuate nucleus (ARC) [21]. Several neurotransmitters are involved in food intake and body weight: serotonin (5-HT), norepinephrine, histamine and dopamine.

5-Hidroxitriptamine Receptors (5-HT)

Of the 5-HT receptors in the human brain, the most involved in mediating food intake are 5 HT1A and 5HT2C but the most studied receptor is 5HT2C. The 5HT2C and 5HT1A agonists have opposite effects on food intake-the 5 HT1A agonist increases food intake [22] and 5HT2C agonist decreases food intake [23]. The 5-HT2C antagonism increases food intake [24] and also attenuates the decrease of food intake produced by the 5-HT2C agonists and sibutramine an inhibitor of serotonin and norepinephrine reuptake. What is surprising, however, is the fact that the correlation between these receptors and the increase in weight is different between the new generations of antipsychotics. Ziprasidone is an antagonist of the 5HT2c receptors but there are no clinical evidence demonstrating weight gain, compared with clozapine and olanzapine which demonstrate the highest weight. Another receptor involved in weight control is 5HT6 antagonist that inhibits food intake. It was shown that 5 HT6 antagonism does not protect against obesity, as antipsychotics with the highest affinity for this receptor, clozapine and olanzapine, show the highest increase in weight. 5-HT1B/2C agonist mCPP produce decreased food intake, possibly by reducing neuropeptide Y (NPY) in the paraventricular nucleus (PVN) of the hypothalamus which is involved in food intake and in regulating body weight being rich in 5-HT2C [25].

Adrenergic receptors

No clear relationship with the propensity to gain weight is apparent: many antipsychotics have effect on α1A receptors and clozapine, quetiapine, risperidone and paliperidone have an effective antagonism on α2A at clinical doses.

Dopaminergic receptors

The D2 antagonism, a joint effect of antipsychotics, can influence eating behaviour, with an increased food intake resulting from the blocking of the hypothalamic D2 receptors [26].

Histaminergic receptors

Antipsychotics have a relative affinity for H1 receptors. Olanzapine with high affinity for the H1 receptors is associated with a high rate of weight gain while ziprasidone and aripiprazole is associated with a low affinity for the H1 receptors is associated with a low rate of weight gain. The 5-HT2C antagonism or inverse agonism in relation to D2 antagonism may be sufficient to explain the effects of olanzapine and clozapine on food intake and body growth.

Dopamine and prolactin

A consequence of the D2 receptor antagonism of antipsychotics is prolactin secretion that can be associated with obesity [27]. Since olanzapine and clozapine have little effect on prolactin, prolactin increase is unlikely to be a contribution to weight gain.

Sedation

The antagonism of α1 adrenergic receptor and H1 histaminergic may contribute to weight gain by physical inactivity.

Diabetes induced by the antipsychotics

A well-established consequence of obesity and of the metabolic syndrome is the development of diabetes. But diabetes can occur also in the absence of obesity in patients treated with antipsychotic producing a ketoacidosis potentially lethal. The fact that the two antipsychotics (olanzapine and clozapine) with the greatest effect on weight gain have also the highest association with impairment of glucose levels may suggest a common pharmacological mechanism. Silvestic and Prous [27] have demonstrated the correlation between the affinity for muscarinic M3 receptor and the ability of antipsychotic medication to cause

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diabetes. They explain the risk for diabetes by the ability of these drugs to block the pancreatic M3 receptor. In the presence of antipsychotics that can block the M3 receptor, glucose-addicted acetylcholine cannot activate the M3 receptor. The plasma level of insulin is insufficient to reduce postprandial hyperglycaemia. Glycaemia remains high; acetylcholine stimulates parasympathetic, releases insulin-a "normalization of basal level of insulin" by increasing insulin synthesis. It reaches the insulin receptors desensitization and the insulin resistance. An increasing number of pancreatic M3 receptors can induce the increase of insulin secretion and therefore insulin resistance. The prolonged hyperglycaemia induces desensitization of glucose transporters resulting glucose intolerance. Hyperglycaemia is associated with an increased risk of beta-pancreatic cell toxicity. Another reason that leads to insulin resistance is also the presence of abdominal adiposity. Antipsychotics have a strong antihistaminic action, H1 receptors are correlated with weight gain.

Pharmacogenetics of weight gain

In the investigation of 5-HT2C promoter polymorphism it was found a significant difference in patients carrying the 759T-allele and-759C/T, being significantly protected against weight gain. 5-HT2C genes and leptin have accumulated most consistency as risk factors for antipsychotic-induced weight gain [28]. Associated with the BDNF polymorphism val66met [29] is an increase in weight in male patients treated with antipsychotics.

Table 1. Mechanisms of metabolic complications of antipsychotic medications [13]

Metabolic complication	Possible mechanism
Weight gain	-Histamine receptor blockade -Blockade of the serotonin receptor 5-HT2C -Aberrant folate metabolism and hyperhomocysteinaemia -Genetic markers, such as 5-HT2C receptors -Brain-derived neurotrophic factor levels
Diabetes mellitus/ hyperlipidaemia	-Weight gain -Disruption of hypothalamic regulation of glucose serum levels -Potent anticholinergic activity -Hyperprolactinaemia -Others: *5-HT2A / 5-HT2C antagonism *Weight gain *Leptin resistance

Table 2. Relative affinities of antipsychotics drugs at some neurotransmitter receptors relevant to metabolic side effects [30]

Dopamine D2 Ki (nM)	Haloperidol 2.0	Clozapine 431	Olanzapine 72	Risperidone 4.9	Paliperidone 9.4	Quetiapine 567	Ziprasidone 4.0	Aripiprazole 0.95	Asenapine 1.0
α1A-adrenergic	0.17 [12]	270 [1.6]	0.66 [109]	0.98 [5.0]	3.8 [2.5]	25 [22]	0.22 [18]	0.038 [25]	1.1 [1.2]
α2A-adrenergic	$< 10^{-2}$ [>1000]	3.0 [142]	0.24 [314]	0.032 [151]	2.0 [4.7]	0.16 [3600]	0.025 [160]	0.012 [74]	[1.3]
Histamine H1	$< 10^{-2}$ [>1000]	220 [2.0]	15 [4.9]	0.96 [5.2]	1.7 [5.6]	76 [7.5]	0.031 [130]	0.032 [28]	1.3 [1.0]
Muscarinic M3	$< 10^{-2}$ [>1000]	17 [25]	1.4 [51]	$< 10^{-2}$ [$>10^4$]	$< 10^{-2}$ [$>10^4$]	0.29 [1943]	$< 10^{-2}$ [>1000]	$< 10^{-2}$ [>1000]	$< 10^{-2}$ [>1000]
5-HT1A	$< 10^{-2}$ [>1000]	4.1(a) [105]	0.036 [2063]	0.011 [427]	0.015 [640]	1.3(a) [430]	0.053(a) [76]	0.17(a) [5.6]	0.52(a) [2.5]
5-HT1B	0.012 [165]	1.1 [398]	0.14 [509]	0.091 [53.6]	0.087 [109]	0.52 [1109]	1.0(a) [4.0]	$< 10^{-2}$ [830]	0.33 [4.0]
5-HT2A	0.035 [57]	81 [5.35]	30 [3.37]	29 [0.17]	4.9 [1.9]	2.8 [200]	13 [0.30]	0.11 [8.7]	18 [0.071]
5-HT2C	$< 10^{-2}$ [>1000]	46 [9.44]	7.2 [10.2]	0.41 [12]	0.20 [48]	0.22 [2500]	0.31 [13]	0.043(a) [22.4]	37 [0.035]
5-HT6	$< 10^{-2}$ [>1000]	25 [17]	12 [6.0]	$< 10^{-2}$ [>1000]	$< 10^{-2}$ [>1000]	0.30 [1864]	0.066 [61]	$< 10^{-2}$ [642]	5.2 [0.25]

A dependent relationship was found between the administrated dose of antipsychotic and the complications of metabolic syndrome (Table 1) [13], as shown in Table 2 [30]. For aripiprazole, quetiapine and ziprasidone this causal relationship does not exist, for risperidone the results are intermediate and for clozapine and olanzapine a very high causal relationship is noticed. [13].

Conclusions

There is no doubt that the metabolic adverse effects associated with the antipsychotic treatment are a clinical concern, remaining an open debate for the discovery of new therapies for improving the lives of patients and life expectancy increasing

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