

Atypical Antipsychotics: Do Their Direct Actions on Adipocytes Contribute to Metabolic Disturbances?

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The introduction of Atypical Antipsychotics (AAP) has improved the treatment of many psychiatric disorders by reducing the incidence of extrapyramidal side effects, but it has come at the expense of developing severe metabolic disturbances. Although the AAP were initially developed for the treatment of schizophrenia, their use has been expanded to include treatment of bipolar disorder, autism, posttraumatic stress disorder, dementia, and as 'off label' therapy for major depression. The current dogma posits that both therapeutic and negative side-effects of the AAP are due to their exclusive actions within the brain. Here we argue that very little consideration has been given to the potential actions of the AAP in peripheral sites, constituting a serious deficit in our understanding of the full spectrum of the biological action of these drugs.

The hyperactive Dopamine (DA) theory of schizophrenia, formulated 60 years ago, was based on the observations that drugs which increase DA caused schizophrenic-like symptoms, while the blockade of DA suppressed these symptoms [1,2]. Conventional (first generation) antipsychotics, e.g., chlorpromazine and haloperidol, antagonize the D2 Dopamine Receptor (D2R) and ameliorated positive symptoms of psychosis. However, their tolerability is limited by severe neurological side effects such as Parkinsonism and tardive dyskinesia [1]. The search for drugs with lesser extrapyramidal side effects led to the development of second generation antipsychotics, or AAP [3]. All AAP share high binding affinity for D2R, but differ from conventional antipsychotics by binding to many other neurotransmitter receptors.

In the last two to three decades, AAP have been increasingly prescribed for a growing list of mental disorders, with 10 different AAPs currently approved for use in the United States [4]. However, the initial optimism with regard to the advantages of AAP over earlier drugs has been tempered by their propensity to induce weight gain and serious metabolic disturbances [1,5,6]. The use of AAP in the management of autism has tripled in the past decade, representing the largest increase of the number of juvenile patients receiving AAP [7]. This should be particularly worrisome, since drug-induced obesity and metabolic disturbances initiated in childhood have a high likelihood of developing into adult type II diabetes and cardiovascular disease later in life [8].

Unlike the typical antipsychotics which primarily antagonize D2R, AAP target other dopaminergic (DAR), serotonergic (5-HTR), histaminergic (HR), adrenergic (AR) and cholinergic (ACR) receptors. Humans have five DAR, sixteen 5-HTR, four HR, five AR, and five AcR receptor genes. Some of these produce multiple receptor proteins via alternative splicing or post-translational modifications, giving rise to more than 40 potential target receptors. A prime example of the promiscuity of these drugs is Olanzapine, which binds at high affinity to the following receptors: serotonin 5-HT2A/2C, D1R, D2R, H1, M1 (muscarinic) and ARa1 receptors [9]. What is commonly overlooked is the fact that expression of the aforementioned receptors is not limited to the CNS. For example, DAR expression occurs in the kidney, gut, cardiovascular system, and adipose tissue [10], with peripheral DA regulating blood pressure, intestinal motility, and metabolic functions. Expression of 5-HTR is found in many tissues that

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include: gastrointestinal, smooth muscle, liver, and adipose tissue, with peripheral serotonin involves in platelet aggregation, vasoconstriction, gut peristalsis, bladder control, and glucose metabolism [11].

The most common metabolic side effect associated with use of AAP is a rapid and significant weight gain. Olanzapine and clozapine, the first AAP put into wide use, cause the most profound increases in body mass, often on the order of 10 kg during the first year of use. Other AAP also trigger weight gain to varying degrees. The AAP-associated weight gain is primarily due to fat mass expansion, causing abdominal (visceral) obesity. Concurrent with the increased adiposity, patients often exhibit other symptoms of metabolic dysregulation such as hypertension, dyslipidemia, and impaired glucose tolerance, all of which are the hallmarks of the metabolic syndrome. The metabolic syndrome in turn, can lead to the development of cardiovascular disease and Type II Diabetes.

Initially, the metabolic effects of the AAP were thought to be due to their action in the hypothalamus and perturbation of the orexigenic and anorexigenic feeding circuits. This hypothesis, however, was formulated before the discovery of functional DAR and 5-HTR signaling in adipose tissue, and the endocrine contribution of adipose tissue to overall metabolic homeostasis. Figure 1 conceptualizes our view of the interactions between the brain and peripheral sites of AAP actions which affect metabolic homeostasis.

Model systems for studying direct peripheral effects of AAP on metabolic regulation are limited. Like humans, treatment of rodents with AAP cause rapid and significant weight gain and other metabolic sequelae [12]. However, existing animal models have two major drawbacks. First, unless such drugs are infused directly into the brain, it is not feasible to separate central from peripheral sites of actions of these agents. Second, the control of feeding behaviour in rodents is different from that of humans. A prime example is leptin, which is produced by adipocytes, and was discovered through analysis of genetically-obese mice. Much to the disappointment of obesity specialists, leptin plays a lesser role in the control of appetite in humans than rodents [13].

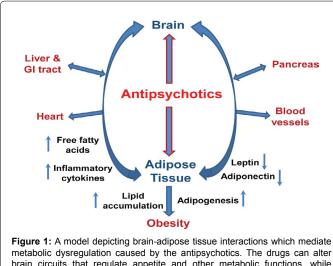
Given that adipose tissue plays a central role in metabolic homeostasis, coupled with the observation that fat cells express multiple AAP targets, adipocytes can be used as a laboratory model for analysing the peripheral actions of the AAP. Viable primary adipocytes can be isolated from both

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metabolic dysregulation caused by the antipsychotics. The drugs can alter brain circuits that regulate appetite and other metabolic functions, while concomitantly having significant effects on multiple adipose tissue functions. Other organs involved in metabolism, including pancreas, liver and GI tract, are also affected, directly or indirectly by the antipsychotics.

human and animal adipose tissue. Additionally, adipocyte precursor cells, or preadipocytes, can be induced to differentiate into functional mature adipocytes *in vitro*. Both regulatory and metabolic endpoints such as adipokine secretion, lipolysis, lipogenesis, and glucose uptake can be assessed in these models. For example, using adipocyte cultures, we reported that DA inhibits leptin release, suppresses lipolysis, and stimulates preadipocyte proliferation [14]. We also found that several 5-HTR subtypes are expressed in human adipocytes, and that serotonin inhibits leptin release (unpublished observation).

In murine 3T3-L1 adipocytes, antagonists of 5-HT2AR and 5-HT2CR inhibited cell differentiation, suggesting a role for serotonin in adipogenesis [15]. Olanzapine and clozapine have been reported to promote lipid accumulation in cultured human adipocytes [16]. Because of the multiple receptors targeted by these drugs, the response to AAP is not straightforward. We have observed non-monotonic dose responses to olanzapine, risperidone, and ziprasidone, using human adipocytes isolated from several patients (unpublished observations). The simplest explanation is a concomitant activation or inhibition of DAR and/or 5-HTR subtypes with increasing concentrations of the AAP.

Most experiments done to date use adipose tissue fragments, isolated primary adipocytes, or *in vitro* differentiated primary preadipocytes. Primary cells have a limited lifespan in culture and are not readily manipulated to eliminate specific DAR or 5-HTR necessary to determine their contribution to fat cell function. Consequently, current *in vitro* models for analysing the effects of AAP on adipose tissue are limited by the lack of appropriate human adipocyte cell lines that are amenable to genetic manipulation by genome editing or RNA interference. In order to truly understand the nature of AAP effects on adipose tissue, we must first clearly define the function of monoamine neurotransmitters in fat cell homeostasis. To do this, better model systems are needed. At best, we can show that AAP directly affect adipose tissue and these effects likely contribute to the weight gain and metabolic derangement associated with many of these drugs. With further studies and better model development, it should be possible to identify how AAP are acting peripherally and synthesize new and effective compounds that lack the disastrous metabolic consequences. Until then, excessive therapeutic use of existing AAP, particularly those prescribed for young patients that are most susceptible to the long-term effects of childhood obesity, should be carefully considered.

References

- Kapur S, Mamo D (2003) Half a century of antipsychotics and still a central role for dopamine D2 receptors. Prog Neuropsychopharmacol Biol Psychiatry 27:1081-1090.
- Carlsson A (1988) The current status of the dopamine hypothesis of schizophrenia. Neuropsychopharmacology 1:179-186.
- Coccurello R, Moles A (2010) Potential mechanisms of atypical antipsychoticinduced metabolic derangement: clues for understanding obesity and novel drug design. Pharmacol Ther 127: 210-251.
- 4. Food and Drug Administration (2016) Atypical Antipsychotic drugs information.
- Pramyothin P, Khaodhiar L (2010) Metabolic syndrome with the atypical antipsychotics. Curr Opin Endocrinol Diabetes Obes 17: 460-466.
- Garver DL (2006) Evolution of antipsychotic intervention in the schizophrenic psychosis. Curr Drug Targets 7: 1205-1215.
- Park SY, Cervesi C, Galling B, Molteni S, Walyzada F, et al. (2016) Antipsychotic use trends in youth with autism spectrum disorder and/or intellectual disability: a meta-analysis. J Am Acad Child Adolesc Psychiatry 55: 456-468.
- Weiss R (2011) Childhood metabolic syndrome: must we define it to deal with it? Diabetes Care 34: S171-S176.
- Farah A (2005) Atypicality of atypical antipsychotics. Prim Care Companion J Clin Psychiatry 7: 268-274.
- Rubi B, Maechler P (2010) Minireview: new roles for peripheral dopamine on metabolic control and tumor growth: let's seek the balance. Endocrinology 151: 5570-5581.
- Berger M, Gray JA, Roth BL (2009) The expanded biology of serotonin. Ann Rev Med 60: 355-366.
- Albaugh VL, Henry CR, Bello NT, Hajnal A, Lynch SL, et al. (2006) Hormonal and metabolic effects of olanzapine and clozapine related to body weight in rodents. Obesity (Silver Spring) 14: 36-51.
- Halford JC (2001) Pharmacology of appetite suppression: implication for the treatment of obesity. Curr Drug Targets 2: 353-370.
- 14. Borcherding DC, Hugo ER, Idelman G, De SA, Richtand NW, et al. (2011) Dopamine receptors in human adipocytes: expression and functions. PLoS ONE 6: e25537.
- Kinoshita M, Ono K, Horie T, Nagao K, Nishi H, et al. (2010) Regulation of Adipocyte Differentiation by Activation of Serotonin (5-HT) Receptors 5-HT2AR and 5-HT2CR and Involvement of MicroRNA-448-Mediated Repression of KLF5. Mol Endocrinol 24: 1978-1987.
- Nimura S, Yamaguchi T, Ueda K, Kadokura K, Aiuchi T, et al. (2015) Olanzapine promotes the accumulation of lipid droplets and the expression of multiple perilipins in human adipocytes. BBRC 467: 906-912.