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Lipogenic effects of psychotropic drugs: focus on the SREBP system

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1. ABSTRACT

Antipsychotics, antidepressants and mood stabilizers are psychotropic drugs widely used in the treatment of psychiatric disorders, such as schizophrenia, bipolar disorder and major depressive disorder. Such drugs have been used since the early 1950s, and it is now well established that they target neurotransmitter receptors and/or transporters located on central nervous system (CNS) neurons. However, their mechanism of action is still not fully understood, and there is large inter-individual variation in therapeutic response. Psychotropic drugs are also associated with numerous adverse effects, of which weight gain and metabolic disturbances have gained increased focus during the last decade. Based on studies in cultured cells, we have demonstrated that several psychotropic drugs upregulate the expression of genes involved in cellular fatty acid and cholesterol biosynthesis, controlled by the SREBP transcription factors. Lipogenic effects were also observed *in vivo*, in rat liver and in lymphocytes from drug-treated patients. These results provide new insight into the molecular mechanisms of psychotropic drug action and could be relevant both for their therapeutic action and metabolic adverse effects.

2. INTRODUCTION

Antipsychotics, antidepressants and mood stabilizers represent cornerstones in the treatment of serious psychiatric disorders, such as schizophrenia, bipolar disorder and major depression. Although their mechanisms of action are not fully understood, they act, at least in part, via neuronal receptors and transporters in the CNS. Antipsychotic effect is primarily mediated via dopamine D2 receptor antagonism in specific brain areas (1, 2). Unfortunately, treatment with first-generation (typical) antipsychotics, such as chlorpromazine and haloperidol, frequently induces extrapyramidal side effects due to strong D2 antagonism in the striatum (3). The discovery of clozapine marked the emergence of a new group of antipsychotics known as second-generation (atypical) agents, which are characterized by a more moderate D2 occupancy and higher affinity to serotonergic 5-HT2 receptors, but with otherwise varied receptor-binding profiles (2). While the more diverse receptor-binding profiles are associated with a reduced risk of extrapyramidal side effects, several of the atypical antipsychotic agents are now recognized to increase the risk of metabolic adverse effects, such as weight gain, dyslipidemia and Type 2 diabetes. Affinity to H1 and 5-

HT2C receptors has been correlated to elevated risk of developing metabolic side effects (8). Clozapine and olanzapine are the agents most strongly associated with these serious side effects (4). Increased adipose tissue mass has been shown to underlie antipsychotic-induced weight gain in patients (5), and it has also been demonstrated in animal studies (6, 7). Although increased food intake is thought to be a major underlying factor for the dysmetabolic features caused by antipsychotic agents, recent studies have demonstrated that certain characteristics, as, for example, dyslipidemia, can occur independent of weight gain, as has been observed in patients treated with clozapine or olanzapine (9, 10).

Similar to the antipsychotics, drugs used to treat major depressive disorder also target monoamine neurotransmitter systems. Tricyclic agents (TCAs) and monoamine oxidase (MAO) inhibitors block the reuptake of monoamines from the synapse or inhibit presynaptic degradation of serotonin and noradrenaline (3). Selective serotonin reuptake inhibitors (SSRIs) have recently become widely used. Drugs with other synaptic effects, such as mirtazepine (a noradrenergic α2 antagonist with complex actions on both noradrenergic and serotonergic neurotransmission) and bupropion (an inhibitor of noradrenaline and dopamine reuptake), are also recognized to have antidepressant effects. Several TCAs, SSRIs and mirtazepine, but not bupropion, are known to increase the risk of weight gain (11, 12). Mood stabilizers, such as lithium, carbamazepine and the modified fatty acid valproate, constitute a third class of psychotropic drugs known to be effective in the prevention of mania and depression in bipolar patients. Weight gain is a recognized adverse effect of several mood stabilizers (12).

Although separate and independent mechanisms of action are evident for different classes of psychotropic drugs, observations from clinical practice suggest that some common properties could exist. For instance, in addition to their use in the treatment of schizophrenia, antipsychotic drugs represent valuable supplements in the treatment of bipolar disorder and major depressive disorder (3, 13). Drug response varies widely between individuals, and thus a better understanding of the molecular mechanisms involved could facilitate personalized treatment, with optimal therapeutic outcome and minimal adverse effects. Furthermore, it could provide valuable information for the development of new types of psychotropic drugs. Our findings of a broad activation of SREBP-controlled gene expression in response to antipsychotic and antidepressant drugs might represent such a common mechanism of action. This review will summarize evidences supporting this hypothesis.

3. ANTIPSYCHOTIC DRUGS INFLUENCE THE EXPRESSION OF LIPOGENIC GENES IN CULTURED CELLS

We aimed at gaining further insight into the mechanisms of psychotropic drug action, investigating whether these agents may possess common signatures of molecular targets. We anticipated that some of their effects could be mediated via alterations at the transcriptional level. Thus, we applied microarray technology to measure global gene expression changes (14). This powerful tool enables the identification of regulated genes and pathways without any *a priori* hypothesis or the need for detailed biological knowledge. We began by investigated human cultured glioma (GaMg) cells exposed to haloperidol (typical, first generation antipsychotic) or clozapine (atypical, second generation antipsychotic) for up to 24 h. Glioma cells were chosen due to the important neuron-supporting role of glial cells and due to practical aspects concerning cell cultivation.

The microarray data revealed that both haloperidol and clozapine upregulated a cluster of genes encoding lipid biosynthetic enzymes (Figure 1) (14). The majority of these genes, including those encoding the rate-limiting enzymes 3-hydroxy-3-methylglutaryl-coenzyme A synthase-1 (HMGCS1) and 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), are involved in the biosynthesis of cholesterol. Several genes encoding enzymes further downstream in the cholesterol biosynthesis pathway were also upregulated (Figure 1). In addition, the genes encoding crucial enzymes in fatty acid biosynthesis, stearoyl-CoA desaturase (SCD) and fatty acid synthase (FASN), were among those upregulated. Interestingly, a previous high throughput gene expression study had demonstrated haloperidol- and clozapine-induced changes in lipid metabolism-related genes in the mouse frontal cortex and striatum (15), although none of these genes were within the cluster of regulated genes identified by us.

In order to investigate antipsychotic-induced stimulation of cellular lipogenesis more thoroughly, we used real time PCR to examine several genes involved in various aspects of lipid homeostasis (16). In cultured GaMg cells, clozapine (0.1 μM – 50 μM) induced marked, dose-dependent transcriptional activation of genes involved in cholesterol metabolism, as for e.g. *HMGCR* and *HMCGS1*, and in fatty acid biosynthesis, as for e.g. *FASN* and *SCD1* (for full designations, see legend to Figure 1). The degree of maximum activation (obtained with 50 μM clozapine) varied markedly between the different genes, with fold-changes ranging from 2.2 to 7.3 (16).

When comparing antipsychotic-induced elevation of lipogenic gene expression across different CNS-derived cell lines, we observed cell-type specific effects. We found that transcriptional activation was most evident in human cultured glioma (GaMg) and astrocytoma (CCF-STTG1) cell lines (16). In addition, we demonstrated the upregulation of lipogenesis-related genes by haloperidol and clozapine in a rat glioma cell line (BT4C) (14). The effect was less pronounced in human cortical neuron cells (HCN2) and in a primary cell culture of the rat hippocampus and almost absent in human neuroblastoma cells (SH-SY5Y) (16). This observation of stronger effect in glioma cells compared to cortical cells is in agreement with the fact that, in the CNS, the majority of cholesterol is produced *de novo* by glial cells (17). The upregulation of lipid biosynthesis genes in human hepatoma cells (HepG2) was similar to the effect in glial cells, suggesting potential

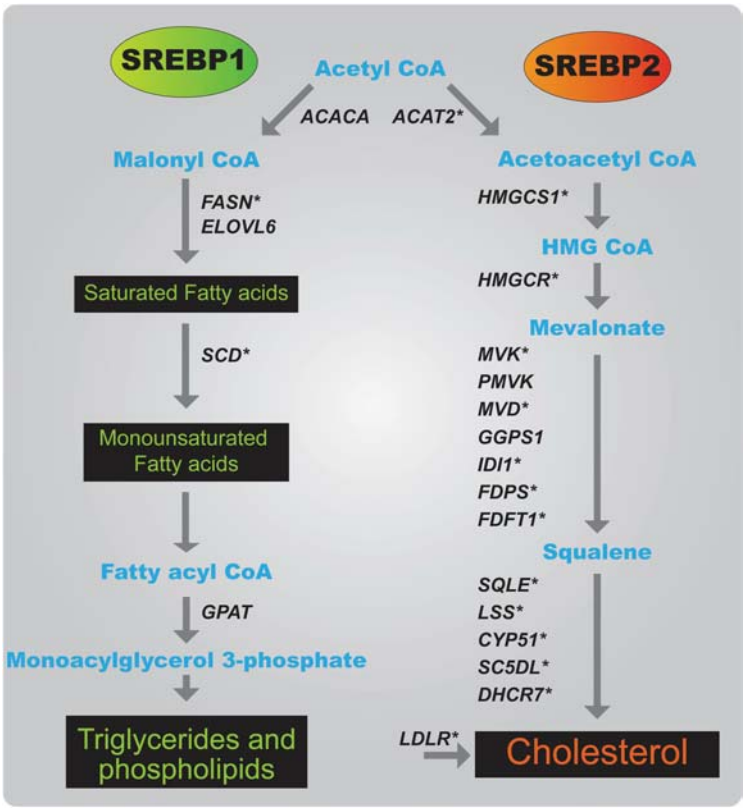

Figure 1. Lipogenesis controlled by the sterol regulatory element-binding protein (SREBP) transcription factor system. The SREBP1 transcription factor preferentially regulates genes involved in fatty acid biosynthesis, including acetyl-CoA carboxylase alpha (*ACACA*), fatty acid synthase (*FASN*), long chain fatty acid elongase 6 (*ELOVL6*), stearoyl-CoA desaturase (*SCD*) and mitochondrial glycerol-3-phosphate acyltransferase (*GPAM*). The SREBP2 transcription factor mainly controls cholesterol biosynthesis and cholesterol uptake genes, including acetyl-Coenzyme A acetyltransferase 2 (*ACAT2*), 3-hydroxy-3-methylglutaryl-coenzyme A synthase-1 (*HMGCS1*), 3-hydroxy-3-methylglutaryl-coenzyme A reductase (*HMGCR*), mevalonate kinase (*MVK*), phosphomevalonate kinase (*PMVK*), geranylgeranyl diphosphate synthase 1 (*GGPS1*), isopentenyl-diphosphate delta isomerase 1 (*IDI1*), farnesyl diphosphate synthase (*FDPS*), farnesyl diphosphate farnesyl transferase 1 (*FDFT1*), squalene epoxidase (*SQLE*), lanosterol synthase (*LSS*), cytochrome P450, subfamily 51 (*CYP51*), sterol-C5-desaturase (*SC5DL*), 7-dehydrocholesterol reductase (*DHCR7*) and low density lipoprotein receptor (*LDLR*). Modified from Horton *et al* (74).

effects of antipsychotic-induced increase of lipogenesis outside the CNS as well (18).

It was important to determine the functional consequences of transcriptional activation of lipid biosynthesis-related genes. We found that the increased *HMGCR* gene expression was accompanied by a moderate increase in HMGCR enzyme activity for both haloperidol and clozapine, as compared to vehicle-treated GaMg cells. In addition, the cellular content of cholesterol and triglycerides was increased after drug exposure (14). Taken together, our results indicated a generalised antipsychotic-induced activation of lipogenesis in glial and liver cells, with less pronounced effects in neuronal cells. Our results from HepG2 cells were recently supported by findings in primary rat hepatocytes, in which clozapine and olanzapine were shown to upregulate several lipogenic genes (including *FASN* and *SCD1*) after 24 h of treatment (19). In addition, these antipsychotics increased intracellular levels of free fatty acids, cholesterol and free cholesterol. In olanzapine-treated cells, triglycerides were also increased. Corresponding findings have been reported in 3T3 cells (preadipocytes) and in isolated rat adipocytes (20, 21). At the same time, however, one study failed to demonstrate that antipsychotic-induced activation of SREBP-controlled gene expression translated into increased cholesterol biosynthesis in cultured cells (22). Thus, further studies are warranted in order to clarify this issue.

4. LIPID BIOSYNTHESIS AND THE SREBP TRANSCRIPTION SYSTEM

The upregulated lipid biosynthesis-related genes are all known to be under transcriptional control of the sterol regulatory element-binding proteins SREBP-1 and SREBP-2, which are major activators and regulators of lipogenesis (Figure 1) (23). SREBP1 (two splice variants: SREBP1a and SREBP1c, both encoded by the SREBF1 gene) and SREBP2 (encoded by SREBF2) are present as 120 kDa inactive precursors in the endoplasmic reticulum (ER) membrane, where they form a complex with the SREBP cleavage activating protein (SCAP) and the insulin

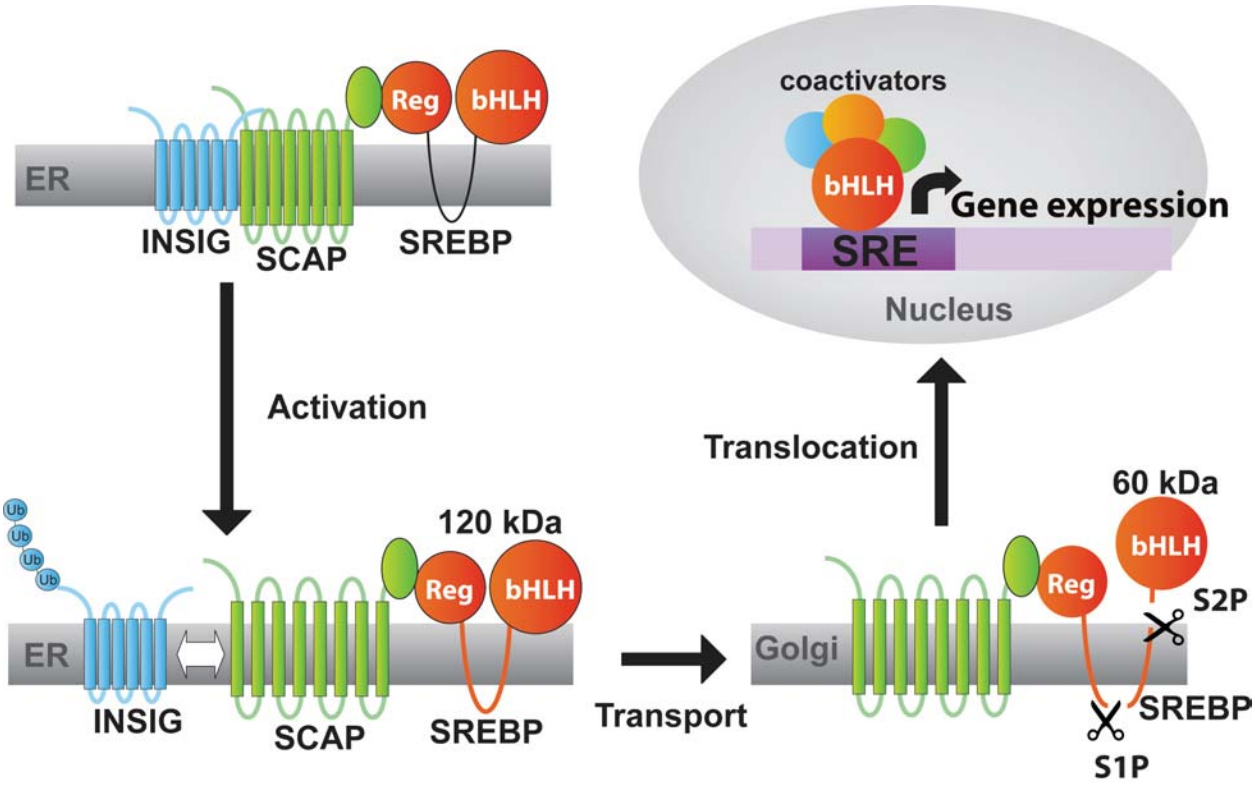

Figure 2. Proteolytic activation of SREBP-controlled lipid biosynthesis. The SREBP transcription factors (red) are synthesized as inactive precursors in the endoplasmic reticulum (ER), where they reside in a complex with the SREBP-cleavage activating protein (SCAP) (green) and the insulin-induced gene (INSIG) (light blue). In the inactive state, interaction between SCAP and INSIG retains the SCAP/SREBP complex in the ER. Upon activation, when sterol levels are low, SCAP undergoes a conformational change and is released from INSIG. SCAP assists the transport of the 120 kDa precursor SREBP to the Golgi apparatus as the initial step in SREBP activation, followed by a two-step proteolytic cleavage involving the Golgi-specific S1P and S2P proteases, thus releasing a 60–70 kDa transcriptionally active N-terminal domain. The mature basic-helix-loop-helix (bHLH) is subsequently translocated to the nucleus, where it activates the expression of genes involved in cholesterol and fatty acid biosynthesis via binding to their sterol regulatory element (SRE).

induced gene (INSIG) proteins (two different isoforms: INSIG1 and INSIG2) (Figure 2). The different SREBP isoforms overlap in function: SREBP1a, which is the predominant variant in cultured cells, regulates the expression of genes involved in both cholesterol and fatty acid biosynthesis, with the latter more efficiently activated, while SREBP1c preferentially controls the expression of fatty acid biosynthesis genes and SREBP2 mainly regulates cholesterol biosynthetic genes (23). Upon activation, the SREBP proteins are escorted to the Golgi by SCAP, followed by a specific two-step proteolysis, producing a mature, transcriptionally active 60–70 kDa SREBP fragment that is subsequently translocated to the nucleus (Figure 2). This basic helix-loop-helix (bHLH) domain of SREBP activates lipogenic gene expression via binding to the sterol regulatory element (SRE), which is found in the promoter region of numerous SREBP target genes.

5. ANTIPSYCHOTIC DRUGS STIMULATE PROTEOLYTIC SREBP ACTIVATION *IN VITRO*

The observed upregulation of lipid biosynthesis genes could, in principle, either be caused by a direct effect of antipsychotic drugs on each gene or be mediated via a common gain controller. Since our global gene expression data strongly suggested SREBP-mediated activation, we measured the cellular levels of transcriptionally active and inactive SREBP proteins (14). Western blot analysis demonstrated that antipsychotic drug exposure of cultured GaMg cells for 3, 6, 16 and 24 h induced a time-dependent elevation of proteolytic SREBP cleavage. A marked increase in the ratio between the 60 -70 kDa mature (i.e. transcriptionally active) bHLH fragment and the 120 kDa membrane-bound, inactive precursor was observed for SREBP2 (Figure 3) and, to some extent, for SREBP1 after exposure to antipsychotic agents. These results, which have been partially replicated by Lauressergues *et al.* (19), strongly suggested that the upregulation of lipogenic gene expression is mediated by antipsychotic-induced SREBP activation.

The drug-induced proteolytic activation of the SREBP system could be mediated as a result of a direct drug effect on the SREBP proteins or via the upregulation of the *SREBF1* or *SREBF2* genes encoding the transcription factors. We therefore examined the time-dependent

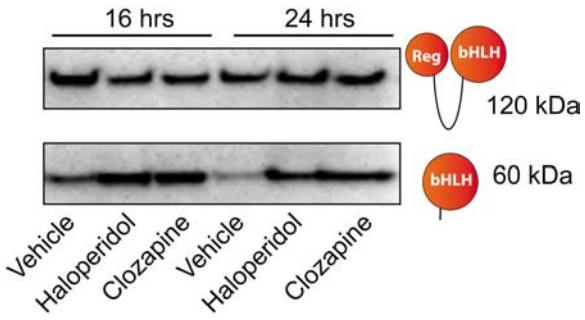

Figure 3. Antipsychotic-induced proteolytic SREBP activation. Proteolytic activation of the SREBP2 transcription factor in cultured GaMg cells after 16 or 24 h of exposure with vehicle (lactic acid), haloperidol (10 μM) or clozapine (30 μM). Both the 120 kDa precursor and the 60-70 kDa transcriptionally active basic helix-loop-helix domain were detected by western blot analysis. The ratio was increased 2-3 fold after exposure to haloperidol or clozapine relative to vehicle. Data from (14).

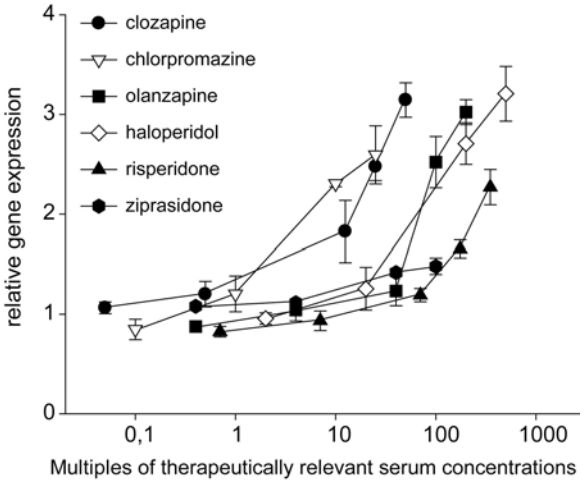

Figure 4. Dose-response curve in antipsychotic-exposed GaMg cells extrapolated to therapeutically relevant serum levels. Dose-dependent activation of SREBP-controlled gene expression (measured as fold-change *HMGCR* expression levels) was determined for each drug. The molar concentrations used in the cell culture experiment were transformed into multiples of therapeutically relevant serum level, determined for each drug according to the AGNP-TDM expert group consensus guidelines (31). Figure from (16).

activation at the protein level, as well as gene expression changes of *SREBF1a*, *SREBF2* and their target genes (14). The proteolytic activation of SREBP1 and SREBP2 and the subsequent upregulation of their target genes, *HMGCR* and *FASN,* were clearly elevated by haloperidol and clozapine as early as 3 h after exposure. In contrast, the *SREBF1a* and *SREBF2* genes displayed minor and, more importantly, clearly delayed responses during the time course experiment, thereby ruling out an initial transcriptional activation of the SREBP-encoding genes. Thus, transcriptional activation of lipid biosynthesis genes seems to be mediated via primary antipsychotic-induced proteolytic activation of the SREBP transcription factors, without any preceding upregulation of the SREBP gene expression.

This delayed upregulation also applied to the cholesterol transport genes Apolipoprotein E (*APOE*); ATP-binding cassette 1, sub-family A, member 1 *(ABCA1)*; Niemann-Pick disease, type C1 (*NPC1)*; Niemann-Pick disease, type C2 *(NPC2)* and Niemann-Pick disease, type C1-like 1 *(NPC1L1)*) after treatment of glial cultured cells with various psychotropic drugs (24). In terms of pathological states, ApoE is primarily known for its role in the risk of developing Alzheimer's disease (25), but a possible role in schizophrenia has also been suggested (26). Three major allelic ApoE variants, namely ApoEε2, ApoEε3 and ApoEε4, exist (27), and differential effects of these allelic variants on neurite outgrowth have been demonstrated *in vitro*, with enhanced outgrowth in response to APOEε3 expression and inhibition of outgrowth with APOEε4 (28). Two of the cell types (HepG2 and SH-SY5Y) in our study have been found to be homozygous for the *ApoE3* variant (29, 30), but potential clinical effects of antipsychotic-induced upregulation of ApoE would be expected to vary with respect to the allelic ApoE variant harboured by the patient.

6. LIPOGENIC EFFECTS *IN VITRO* AS A COMMON PROPERTY OF ANTIPSYCHOTIC DRUGS

In order to investigate whether drug-induced elevation of lipogenic gene expression is a general feature of antipsychotic drugs, we compared six different antipsychotic drugs (chlorpromazine, haloperidol, clozapine, olanzapine, risperidone and ziprasidone) with regard to their ability to activate the expression of the SREBP target genes *HMGCS1*, *HMGCR*, *SC5DL* and *LDLR* (16). Exposure of GaMg cells to various concentrations (0.1, 1, 10 and 25 μM) of each drug demonstrated that clozapine and haloperidol, and, to a lesser extent, olanzapine and chlorpromazine, clearly enhanced the transcription of these genes, while risperidone and ziprazidone induced minor activation. These drug-induced transcriptional differences are interesting, but great care should be taken when attempting to extrapolate *in vitro* data to a clinical setting. With respect to their individual propensity to activate SREBP-controlled gene expression, it should be noted that antipsychotic drugs vary considerably with respect to their therapeutically relevant serum levels. In an attempt to evaluate the potential clinical relevance of the drug-induced lipogenic upregulation, we transformed the molar concentrations used in the cell culture experiment into multiples of the therapeutically relevant serum concentration for each drug, as defined by the AGNP-TDM expert group consencus guidelines (31) (Figure 4). The transformed data illustrate that, although all drugs stimulated lipogenic gene expression at some concentrations (measured as degree of *HMGCR* upregulation), only clozapine and chlorpromazine induced significant lipogenic activation in the cell cultures within a

range close to clinically relevant concentrations, i.e. 5-10 times above their therapeutic serum levels. Given that therapeutically relevant concentrations in the CNS have been demonstrated to be 10-30 times higher than the serum concentrations (32, 33), our transformation suggests that antipsychotic-induced activation of lipogenic gene expression could be of clinical relevance, at least for clozapine and chlorpromazine. A recent comprehensive microarray study, which included 18 antipsychotic agents, replicated our findings (34). In retinal pigmental epithelial and glioblastoma cell lines, lipogenic genes were found to be clearly overrepresented among transcriptionally induced genes after 24 h of exposure to either typical or atypical antipsychotic agents, using standard drug concentration of 10 μM. The induction of lipogenesis was suggested to be a property that characterizes antipsychotics as a class, with atypical drugs generally having less potent effects. The propensity to induce transcription of lipogenic genes was not correlated to the relative risk of the different drugs to induce metabolic adverse effects, and the authors hypothesized that lipogenic activation was likely to be more relevant to the therapeutic effects of antipsychotic agents. However, the authors did not take into account the considerable variation in therapeutically relevant serum concentrations between the different antipsychotic agents, with serum levels of atypical agents normally in a higher range than typical drugs.

7. SREBP ACTIVATION: A SHARED FEATURE AMONG DIFFERENT CLASSES OF PSYCHOTROPIC DRUGS

Most psychotropic drugs belong to the chemical class of cationic amphiphiles or related substances and share particular physical properties resulting from a chemical structure containing a hydrophilic ring and hydrophobic regions (35). Common structural properties might be of relevance to the overlapping use of such drugs in clinical practice. Amphiphatic compounds have been demonstrated to promote activation of cholesterol biosynthesis by interfering with intracellular cholesterol trafficking and reduce cholesterol levels in the ER (36). Based on our assumption that the antipsychotic-induced stimulation of cellular lipid biosynthesis could represent a new mechanism of drug action, we investigated several other psychotropic drugs, including antidepressants and mood-stabilizers, for their potency to induce an activation of SREBP-controlled lipogenic gene expression in cultured human glioma cells (GaMg) (37). With respect to the antidepressants, we investigated tricyclic antidepressants (amitriptyline, imipramine and clomipramine), selective serotonin reuptake inhibitors (citalopram and fluoxetine), mirtazepine, and bupropion. Of the mood stabilizers, we investigated lithium, valproate and carbamazepine. All antidepressant drugs induced proteolytic SREBP activation with subsequent upregulation of lipogenic genes, but to variable degrees (37). The TCAs had the strongest effect on SREBP-controlled gene expression, while the SSRI citalopram displayed a marked effect at high concentrations. Weak to moderate effects were observed for fluoxetine, bupropion and mirtazepine, whereas the mood stabilizers did not affect SREBPs proteolytic cleavage or any downstream genes (37). These results link antidepressants, but not mood stabilizers, to SREBP-mediated activation of cellular lipogenesis, reflecting the molecular similarity between antipsychotic and antidepressant drugs. Thus, we theorize that the ability to induce lipogenesis is a shared feature of several psychotropic drugs, independent of the conventional drug classification used in clinical practice.

8. LIPOGENIC EFFECTS OF PSYCHOTROPIC DRUGS *IN VITRO*: A NOVEL MECHANISM OF ACTION?

Several lines of evidence point towards myelin dysfunction in the aetiology of both schizophrenia and bipolar disorder. Neuroimaging and neuropathological studies have revealed myelin deficits, and a number of recent global gene expression studies have demonstrated that several genes involved in myelination are downregulated in post-mortem brain tissue from patients with schizophrenia or bipolar disorder (38, 39). Glia-produced cholesterol can serve as a growth factor to promote synaptogenesis and myelination, and, indeed, recent findings from both schizophrenic patients (40) and from a rat model of demyelination (41) have demonstrated positive effects of antipsychotic drugs on reduced mylination. Therapeutic effect of increased cholesterol biosynthesis may not be directly related to what is generally considered to be group-specific antipsychotic- or antidepressant drug effects. Instead, it might be linked to some common deficit present in both schizophrenia and major affective disorders, e.g. cognitive deficits (42). This possibility is further underscored by the therapeutic breadth of these classes of drugs, with antipsychotic drugs frequently used in treatment of bipolar patients or patients with major depressive disorder (3, 13). Due to the important role of cholesterol in myelination (43, 44), we hypothesized that SREBP-mediated stimulation of the cholesterol and fatty acid biosynthesis in glial cells may represent a novel and clinically relevant action of psychotropic drugs.

Our finding of antipsychotic- and antidepressant-induced activation of lipogenesis may also shed new light on the mechanisms underlying obesity, dyslipidemia and other features of the metabolic syndrome associated with the use of many psychotropic drugs. Serious metabolic side effects are particularly prevalent during treatment with some atypical antipsychotic drugs, such as clozapine and olanzapine, and with the tricyclic antidepressants (4, 45, 46). Of the antipsychotics, we found that clozapine was a powerful SREBP activator, whereas ziprasidone, which is generally considered weight neutral, did not activate the SREBPs. Among the antidepressants, imipramine and amitriptyline are most markedly associated with weight gain, and these drugs also strongly activated the SREBP transcription factors. Furthermore, no SREBP activation was evident following exposure to the assumingly weight neutral agents fluoxetine or buproprion. Apparently, there are some notable exceptions from the correspondence between *in vitro* drug-induced SREBP activation and clinically observed weight gain, especially with respect to

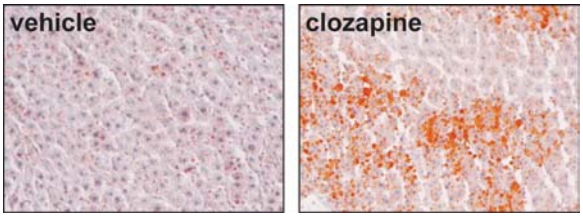

Figure 5. Clozapine-induced lipid accumulation in the liver. Microphotographs of liver tissue sections from female SD rats, 48 h after a single intraperitoneal dose of clozapine (50 mg/kg) or vehicle (lactic acid; 6 µg/ml). Original magnification × 50. The visualization is representative of images obtained from five clozapine-treated and five vehicle-treated rats. Reprinted from (58) with permission.

the mood stabilizers. However, it should be noted that the clinical pattern of weight gain induced by certain mood stabilizers seems to differ from the nature of weight gain caused by antipsychotics or antidepressants. For instance, for valproate, it has been observed that body weight increases more slowly than with antipsychotic drugs (47). Furthermore, lithium is known to cause fluid retention and oedema (48), in contrast to the expansion of adipose tissue observed after treatment with antipsyhotics (5-7). It should also be kept in mind that several recent findings have suggested that psychotropic-induced dyslipidemia may occur independent of obesity, indicating that the underlying molecular mechanisms are more diverse than formerly thought (9, 10). Overall there seems to be partial correspondence between our observed drug-induced SREBP activation and weight gain during drug treatment as reported in the literature (12, 49).

9. ANTIPSYCHOTIC-INDUCED EFFECTS ON SREBP-CONTROLLED GENE EXPRESSION *IN VIVO*

Changes in SREBP activity in peripheral tissues can cause pronounced metabolic disturbances, as demonstrated by hepatic steatosis and severe insulin resistance in rodents overexpressing SREBP1 in liver and in adipose tissue (50-52). Furthermore, the SREBP system is known to interact and cross-talk with other important mediators of metabolic control, such as the transcription regulators peroxisome proliferator activated receptors (PPARs) and liver X receptors (LXRs) (53-56). In order to explore the effects of antipsychotic drugs in an animal model, a single intraperitoneal injection of clozapine or vehicle was administered to rats (57). A high dose was chosen to challenge the SREBP system, as well as to compensate for the markedly shorter half-life of antipsychotic drugs in rats as compared to humans (58, 59). We observed hepatic upregulation of several SREBP target genes, evident as early as 1 h after the clozapine injection. However, in contrast to the sustained antipsychotic-induced SREBP activation seen in human cell cultures, this early phase of enhanced SREBP-controlled gene expression was followed by a marked and prolonged downregulation of all examined SREBP target genes, corresponding to diminished serum drug concentrations (57). This extended phase of downregulated gene expression could be due to negative feedback mechanisms, possibly related to the initial high dose of clozapine (57). We therefore designed an experiment with a lower, but still potent, dose of clozapine, and included earlier time points. Indeed, a more pronounced and statistically significant initial upregulation of lipogenic gene expression was observed in this second experiment. Still, in agreement with the observations from the high-dose experiment, the initial upregulation was followed by a subsequent, marked downregulation (57).

Since the striking *in vivo* effect of clozapine on SREBP-controlled gene expression differed somewhat from our *in vitro* observations, we searched for lipid-related functional consequences of the transcriptional pattern. Indeed, a pronounced increase in liver triglycerides, cholesterol and phospholipids was evident in both rat experiments (57). Hepatic accumulation of lipids was most pronounced in the high-dose experiment at 48 h, visualized by staining of neutral lipids, such as triacylglycerols and cholesteryl esters, in liver sections with Oil red O staining (Figure 5).

The apparent paradox of hepatic lipid accumulation and concomitant lipogenic downregulation led us to examine the expression levels of genes involved in other aspects of lipid homeostasis, such as fatty acid oxidation and cholesterol efflux, including genes controlled by the PPAR and LXR transcription factors (57). In rat liver, acyl-Coenzyme A oxidase 1 (*Acox1*) and ATP-binding cassette 1, sub-family A, member 1 (*Abca1*) (involved in fatty acid oxidation and cholesterol transport, respectively), displayed expression patterns similar to those of the SREBP target genes, but with clearly delayed phases of both up- and downregulation. In addition, we investigated the expression of genes involved in lipolysis and cholesterol esterification. The sterol O-acyltransferase-1 (*Soat1*; involved in the formation of cholesterol esters from excess free cholesterol) gene displayed a rapid and extensive, but transient 4- to 5-fold increase in both experiments, whereas the expression of hepatic lipase (*Lipc*) and hormone sensitive lipase (*Lipe*) (encoding enzymes involved in the breakdown of triacylglycerides, fatty acids, and phospholipids) were significantly downregulated throughout the time course. Interestingly, the minimum expression levels of the lipase genes correlated rather well with the maximum triacylglycerol values, suggesting lipase downregulation as a relevant cause of the observed lipid accumulation. Increased lipid uptake from adipose tissues could also contribute to the phenotype and should be explored in future studies. Taken together, these data provide support for clozapine-mediated perturbation of lipid homeostasis in peripheral tissues as a molecular mechanism involved in antipsychotic-associated metabolic adverse effects and underscore the relevance of cross-talk between SREBP-, PPAR- and LXR transcription factors (60).

Based on our studies in cell cultures and rats, we proposed drug-induced SREBP activation as a relevant mechanism for psychotropic drugs in a clinical setting. In a sample of patients with psychotic disorders, we examined

SREBP-controlled gene expression in peripheral blood cells from 19 olanzapine-treated (continuous monotherapy with olanzapine for at least 3 weeks prior to testing) compared to 19 unmedicated (no use of pharmacological agents in the last 3 weeks prior to testing) patients from an ongoing naturalistic study (61). The groups were matched on gender, race and body mass index (BMI), all of which are known to be of importance for lipid levels. We observed a 50-60% increase in the expression of the SREBP-controlled fatty acid biosynthesis genes *FASN* and *SCD* in patients treated with olanzapine. This finding suggests a direct effect on lipogenic gene expression of olanzapine in peripheral blood cells, independent of weight gain (61). Our cross-sectional study, with BMI-matched groups, was not designed to detect differences in lipid parameters, and there was no significant correlation between gene expression and lipid levels. However, other studies have shown that blood lipid levels in healthy human subjects were correlated with SREBP-regulated gene expression in leukocytes (62).

10. GENETIC VARIATION IN SREBP-RELATED GENES IS RELEVANT FOR METABOLIC ADVERSE EFFECTS AND DISEASE SUSCEPTIBILITY IN PATIENTS WITH SCHIZOPHRENIA

The degree of weight gain induced by antipsychotic drugs is highly variable among individuals, and epidemiological findings suggest that genetic factors play a major role in terms of risk factors (63). From our convergent functional genomic approach, using cellular models to demonstrate that antipsychotics activate the expression of lipid biosynthesis genes controlled by the SREBP transcription factors, we hypothesized that the major genes involved in the SREBP system (*SREBF1*, *SREBF2*, *SCAP*, *INSIG1* and *INSIG2*) would be strong candidate genes for inter-individual variation in drug-induced weight gain. In a sample of 160 German patients with schizophrenia, who had been monitored with respect to changes in body mass index during antipsychotic drug treatment, we found a strong association between markers localized within or near the *INSIG2* gene and antipsychotic-related weight gain (64). The association observed by us was most pronounced for the retrospectively recorded increase in BMI (that is, from the very first use of antipsychotic drugs to the inclusion in the study), but it was also clearly evident for the prospectively measured weight gain following clozapine therapy. The mean increase in the retrospectively measured BMI was 1.8±2.3 for the AA carriers (N=129), as compared to 4.1±3.9 for the AC (N=22) and CC (N=1) carriers, which represents an actual weight gain of about 5.2±6.6 kg and 11.8±11.2 kg, respectively, for a person of 170cm height. This trend corroborates a recent report that most of the antipsychotic-induced weight gain is displayed in the first year of treatment with much less increase during the next 7 years (65). The validity of our finding is supported by the fact that 1) this candidate gene was selected a priori by us due to its involvement in antipsychotic-induced SREBP-mediated activation of lipid biosynthesis in cultured cells; 2) the association was observed with several markers which are not in complete LD; 3) the association was found in both the retrospective and prospective recording of antipsychotic-related weight gain in the sample and 4) *INSIG2* has been independently implicated as a susceptibility gene in obesity in several populations (66). Taken together, these findings add to the evidence implying that drug-induced SREBP-mediated activation of cellular lipogenesis is among the underlying mechanisms of antipsychotic-related metabolic adverse effects.

Considering the importance of the SREBP transcription factors in lipid biosynthesis and their possible involvement in antipsychotic drug effects, we hypothesized that genetic variants of *SREBF1* and/or *SREBF2* could affect the risk of developing schizophrenia. Interestingly, when conducting an association study in a large German sample (N=1527), we identified association between schizophrenia and five markers in *SREBF1* and five markers in *SREBF2* (67). Follow-up studies in two independent samples of Danish (N=1436) and Norwegian (N=456) origin (part of the Scandinavian Collaboration on Psychiatric Etiology study, SCOPE) replicated the association for the five *SREBF1* markers and for two markers in *SREBF2* (67). This finding strengthens the hypothesis that dysfunctions in SREBP-controlled cholesterol biosynthesis in the brain may be involved in the aetiology of schizophrenia. No other association studies have yet been reported for these genes. With the imminent release of genome-wide association data on large sets of cases and controls by the Psychiatric Genetic Consortium (https://pgc.unc.edu/index.php), it will be possible to interrogate the role of these genes in schizophrenia at the gene level, but also at a broader cholesterol synthesis pathway level. Interestingly, at the pathway level, several studies have implicated the involvement of myelin related pathways (which are highly correlated to cholesterol since cholesterol is the basic component of myelin) and lipid metabolism pathway in schizophrenia either in post-mortem studies from brain of patients with schizophrenia (38) or in positional candidate genes analysis of linkage meta-analysis (68, 69). Furthermore, serum mRNA levels of *ApoE* and the SREBP2 target gene *Idh1* have recently been pointed out as highly interesting candidate biomarkers for delusional symptoms (70).

11. PERSPECTIVES

Our results, which show a broad activation of SREBP-controlled gene expression by both antipsychotics and antidepressants, provide new insight into the molecular mechanisms of psychotropic drugs. Enhanced cholesterol synthesis in the CNS may be therapeutically beneficial, whereas increased lipid production in the liver and fatty tissue may be linked to the metabolic adverse effects of these drugs. Psychotropic-induced weight gain and associated metabolic dysfunction is generally thought to be caused by increased food intake, mediated via binding to specific receptors in the CNS. Still, recent studies have shown that some drug-induced metabolic disturbances, such as dyslipidemia, can occur independent of weight gain, suggesting a direct effect of psychotropic drugs on lipid metabolism in peripheral tissues. These findings suggest a

clinically relevant role for increased lipid production in antipsychotic-induced metabolic adverse effects.

Recently, several lines of evidence have indicated that alterations in fatty acid metabolism in the hypothalamus can affect satiety and control of food intake (71, 72). This gives rise to the possibility that psychotropic-induced changes of lipid metabolism at this level could also be relevant for the drug-associated hyperphagia and weight gain. Further studies on how psychotropic drugs influence lipid metabolism in the CNS and in peripheral tissues should provide a better understanding of their respective impact on metabolic adverse effects.

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