Effects of psychotropic drugs on Nuclear Factor kappa B

A. TROIB[1], A.N. AZAB[2,3]

[1]The Shraga Segal Department of Microbiology and Immunology, [2]Department of Nursing, [3]Department of Clinical Biochemistry and Pharmacology; Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel

Abstract. – Mental disorders affect millions of people worldwide and are associated with a huge suffering and unbearable burden for patients and their care givers. The pathophysiology of mental disorders is not fully understood. In recent years, accumulating data suggest that inflammation may play a role in the pathogenesis of these illnesses and that psychotropic drugs exert some anti-inflammatory effects. Nuclear Factor κB (NF-κB) is a cellular pathway that has a prominent influence on immune and inflammatory responses in humans. Numerous studies examined the effects of psychotropic drugs on different inflammatory mediators (particularly cytokines) both *in vitro* and *in vivo*. However, relatively few studies investigated the effects of those drugs on NF-κB. This is quite surprising considering the pivotal role of NF-κB in promoting inflammation. The aim of this article is to review the data over the effects of psychotropic drugs on the NF-κB pathway.

Overall, the summarized studies suggest that some psychotropic drugs (such as lithium and imipramine) exert potent inhibitory effects on NF-κB, while the results on other drugs are not conclusive and occasionally contradicting. The discrepancy in the results of different studies seems to derive from the various experimental conditions under which the drugs were tested.

Key Words:
    Antidepressants, Antipsychotics, GSK-3, Lithium, Mood stabilizers.

Introduction

Mental disorders constitute the leading cause of global burden of disease[1,2]. The biological bases and pathophysiological mechanisms underlying these disorders are still elusive. In recent years, a large body of data has accumulated suggesting that inflammation plays a role in the pathogenesis of many mental illnesses[3-15]. Consistently, numerous studies have shown that many psychotropic drugs alter the levels of inflammatory mediators under various experimental conditions[16-21].

Despite the evidence linking inflammation to the pathogenesis and treatment of mental disorders, the mechanism by which particular inflammatory mediators contribute to psychiatric symptoms such as psychosis, anxiety, mania or depression is not understood. Many mediators and cellular cascades contribute to inflammatory processes of the brain, an important one of which is nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). Nuclear Factor κB plays a pivotal role in cancer pathophysiology[22], however, it has also been associated with several mental disorders[3,5,6,8-14]. For example, Sun et al[3] reported that gene expression of components of the NF-κB complex were significantly higher among bipolar disorder patients as compared to control healthy subjects. Similar findings were obtained in the study of Rao et al[6] on postmortem brains of bipolar patients and that of Barbosa et al[14] which examined NF-κB activation in peripheral blood mononuclear cells of bipolar patients. Moreover, a number of studies have shown that levels of components of the NF-κB complex and/or activation of NF-κB were significantly increased in patients with schizophrenia as compared to control subjects[5,8,9,11,12].

The purpose of this article is to review the effects of psychotropic drugs (including mood stabilizers, antidepressant and antipsychotic drugs) on the NF-κB system.

Nuclear Factor κB Pathway

Nuclear Factor κB is a transcription factor that plays a key role in regulating the immune response and is found in most cell types. Mammalian NF-κB family consists of 5 family members: p50, p52, p65 (RelA), c-rel and RelB; those

Corresponding Author: Abed N. Azab, Ph.D; e-mail: azab@bgu.ac.il

control both healthy and pathogenic immune responses[23,24]. Nuclear Factor κB has conserved N-terminus of approximately 300 amino acids, termed Rel homology domain (RHD). Through RHDs, NF-κB interacts with IκBα/IκB$_β$ (inhibitors of κB) proteins, and upon activation, enters the nucleus and bind to DNA[24,25]. At resting conditions, NF-κB resides in the cytosol while it is bound to IκB, which inhibits its activity by preventing its translocation into the nucleus. Phosphorylation of IκB leads to dissociation of NF-κB from IκB and translocation of NF-κB to the nucleus for target gene transcription, while IκB goes to poly-ubiquitination and degradation[23-27]. Toll-like receptors (TLRs), tumor necrosis factor α (TNF-α), interleukin 1β (IL-1β) and tissue damage response are important factors that activate NF-κB[26]. Those factors activate IκB kinase complex (IKKα/ IKK$_β$/ IKKγ and NEMO) leading to phosphorylation of IκB[23-27]. Activation of the NF-κB pathway is illustrated in Figure 1.

Nuclear Factor κB activation is controlled by two pathways: the canonical and the atypical. In the canonical pathway, proteasomal degradation of IκB mediates the activation of NF-κB[28]. In the atypical pathway, NF-κB activation involves p105 or p100. In the p100-mediated pathway, agonist stimulation activates IKKα phosphorylation of p100, which leads to polyubiquitination and partial proteolysis of p100 in the proteasome.

The product of this partial proteolysis is p52, which translocates to the nucleus together with RelB to start gene transcription[29]. The p105 pathway involves constitutive partial proteolysis of p105 in order to produce active p50 subunit. Nuclear factor κB is considered as a pro-survival and pro-inflammatory pathway as it controls the expression of nearly 200 genes among them are many cytokines, growth and transcription factors, and apoptosis regulators[24].

Effects of Psychotropic Drugs on NF-κB

Mood Stabilizers

Lithium

Lithium is the gold standard treatment for bipolar disorder[30]. The therapeutic mechanism of action of lithium is not fully understood. It acts through modulation of several homeostatic mechanisms such as autophagy, oxidative stress, inflammation and mitochondrial function. These responses may be secondary to two key effects: inhibition of inositol monophosphatase which leads to depletion of *myo*-inositol levels[31] and inhibition of glycogen synthase kinase-3β (GSK-3β)[32-34]. However, lithium affects multiple other proteins and cellular pathways and it is not known if one (or more) of these is crucial to its

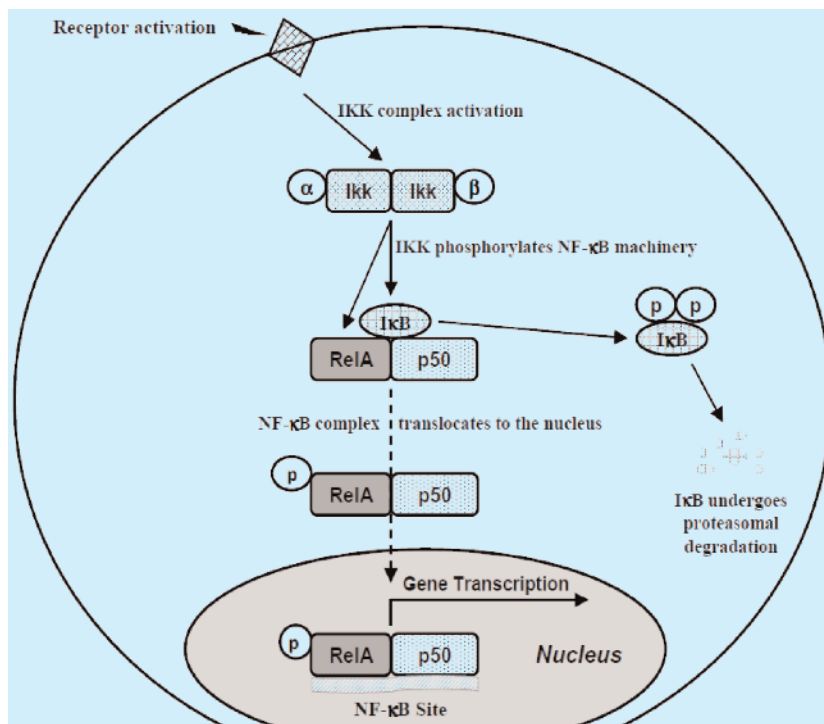**Figure 1.** *A simple illustration of the NF-κB pathway*. In the cytoplasm NF-κB is bound to IκB. Receptor activation by different stimulants activates the IKK complex. IKK phosphorylates IκB leading to dissociation (from it) and translocation of NF-κB to the nucleus. In the nucleus, NF-κB regulates different genes transcription and promotes cellular proliferation, adhesion, survival and inflammatory responses. Abbreviations: IκB, inhibitor kappa B; IKK, inhibitor kappa B kinase; NF-κB, nuclear factor kappa B.

therapeutic efficacy. In this regard, a large body of data has suggested that lithium affects various inflammatory responses. A recent review reported that lithium exerts anti-inflammatory effects such as suppression of cyclooxygenase-2 (COX-2) expression, inhibition of IL-1β and TNF-α and enhancement of IL-2 and IL-10 synthesis[21]. One of the proposed mechanisms for the anti-inflammatory effects of lithium is its ability to inhibit the GSK-3β/NF-κB pathway[21]. Hoefilch et al[35] were the first to demonstrate that GSK-3β facilitates the activity of NF-κB. They treated wild type embryonic fibroblasts with lithium and observed reduced transactivation of NF-κB. Consistently, they found that embryonic fibroblasts from GSK-3β knockout mice had reduced transactivation of NF-κB[35]. In line with these findings, Martin et al[36] showed that GSK-3β inhibition by lithium reduced the binding of p65/p50 to their response element, leading to decreased NF-κB transcriptional activity. Xia et al[37] demonstrated that GSK-3β inhibition by chronic lithium treatment significantly down-regulated the activity of NF-κB in liver of ischemia/reperfusion injury mice. Lithium treated mice showed reduced nuclear accumulation of p65. IκB degradation was elevated in these mice while chronic lithium treatment inhibited this elevation[37]. Moreover, acute and chronic lithium treatment inhibited the expression of anti-apoptotic genes that are regulated by NF-κB such as TRAF2, cFLIP, Bfl-1and cIAF2[37]. In human colorectal cancer cells lithium increased cell apoptosis and reactive oxygen species production through inhibition of the GSK-3β/NF-κB pathway[38]. Lithium treatment reduced expression of NF-κB and its anti-apoptotic target gene Bcl-2 and increased generation of intracellular reactive oxygen species[38]. Furthermore, in a commonly used model for parkinson's disease, astrocytes that were exposed to 6-Hydroxydopamine (6-OHDA) showed an increased pro-inflammatory response[39]. When astrocytes were pretreated with lithium before the exposure to 6-OHDA, it abolished the increased pro-inflammatory response. The anti-inflammatory effect of lithium on astrocytes was mediated through inhibition of the GSK-3β/NF-κB pathway[39]. Lithium treatment reduced nuclear p65 levels in 6-OHDA-treated astrocytes, which was accompanied by a decrease in COX-2, prostaglandin E2 (PGE2) and TNF-α levels[39]. In human periodontal ligament tissue-derived mesenchymal stem cells (PDLSCs) impaired regulation of β-catenin signaling causes a defect in the differentiation potential of the cells. It was demonstrated that GSK-3β acts as a mediator of NF-κB and β-catenin signaling and regulates osteogenesis of PDLSCs, while treatment with lithium significantly reduced NF-κB activity (through inhibition of p65 phosphorylation)[40]. Furthermore, GSK-3β was shown to be a key regulator of TLR signaling associated with the excessive inflammatory response seen in chronic colitis[41]. Inhibition of GSK-3β by lithium resulted in a shift from NF-κB activity to an increase in nuclear cAMP response element-binding (CREB) activity, which attenuated the pro-inflammatory TLR-mediated immune response[41]. In the pathogenesis of atherothrombosis endothelial cells transform to a thrombogenic and inflammatory phenotype. Eto et al[42] have shown that GSK-3 is essential for TNF-α–induced NF-κB activation and subsequent induction of tissue factor (TF) and VCAM-1 expression in human endothelial cells. Lithium significantly reduced both TF and VCAM-1 induction by TNF-α, attesting for a potential therapeutic benefit of lithium therapy[42].

In summary, the reviewed studies suggest that lithium inhibits NF-κB activity and reduce its pro-inflammatory and anti-apoptotic effects. It is worth noting however that contradicting results have also been reported[43-45].

Valproate

Valproate (valproic acid, VPA) is a useful anticonvulsant drug that exerts therapeutic benefits as a treatment for bipolar disorder[30,46]. Similar to lithium, VPA also affects many proteins and signaling cascades[47]. For example, it alters gamma amino butyric acid transmission[47,48], reduce excitatory amino acid-mediated neuronal excitation[49], inhibits histone deacetylases (HDACs)[47,50], inhibits GSK-3β[47,51] and blocks voltage-gated sodium and T-type calcium channels[47,52,53]. Moreover, VPA influences processes of inflammation, oxidation and malignancy[52].

On 2000, Ichiyama et al[54] demonstrated a connection between VPA and NF-κB. They showed that VPA suppresses TNF-α and IL-6 production by inhibiting NF-κB activation in human monocytic leukemia cells and in human glioma cells. Valproate reduced nuclear p65 and p50 levels but had no effect on IκB[54]. Similarly, Rao et al[55] showed that chronic administration of VPA to rats at a therapeutically relevant concentration resulted in a significant reduction in NF-κB binding to the DNA in the frontal cortex. VPA treat-

ment decreased p50 and COX2 while it had no effect on CREB activity[55]. Noh et al[56] tested the effect of HDAC inhibition by VPA in a rat model of Alzheimer's disease. VPA treatment reduced NF-κB and IL-β mRNA levels in the blood. The authors associated these results to VPA inhibition of HDAC[56]. Nuclear Factor κB is constitutively activated in thyroid carcinomas, which is associated with aggressive tumor growth and treatment resistance. In human thyroid cancer cells, VPA treatment dose-dependently reduced activation and DNA binding of NF-κB[57]. Valproate reduced p50 levels and inhibited phosphorylation of IκBα[57]. Furthermore, loss of blood-brain barrier (BBB) integrity induced by focal cerebral ischemia is a major reason for brain damage. In a rat model of focal cerebral ischemic VPA decreased brain infarct volume and exhibited potent anti-inflammatory properties[58]. The BBB protection by VPA involved HDAC inhibition-mediated suppression of NF-κB activation as seen by the translocation of p65 subunit[58]. In a lipopolysaccharide (LPS)-induced acute lung injury model in mice, p65 subunit levels and NF-κB activity were decreased following VPA treatment[59]. The authors suggested that inhibition of NF-κB by VPA is mediated through a HDAC3-dependent mechanism[59]. In a study on macrophage cells, Tsolmongyn et al[60] have shown that VPA reduces LPS-induced inflammatory response by decreasing NF-κB activity and expression of NF-κB target gene Bcl-2. Subsequently, the same group showed that VPA does not directly affect phosphorylation of IKKα/β, IκBα or p65 subunit but rather decrease p65 mRNA synthesis[61]. Although the studies cited above suggested that VPA inhibits NF-κB activity, Go et al[62] reported that VPA enhanced degradation of IκBα leading to increased activation of NF-κB. The effects of VPA on NF-κB were accompanied by a reduction in cell death of neural progenitor cells cultured from embryonic brains of rats[62].

Taken together, the summarized data suggest that VPA inhibits the activity of NF-κB, possibly through inhibition of HDAC.

Carbamazepine

Carbamazepine (CBZ) is an anticonvulsant drug which is also used as a mood stabilizer[30,46]. The mechanism of action of CBZ involves inhibition of Na$^+$ and Ca^{2+} channels permeability[63], among other effects. In recent years, accumulating evidence attests for a possible mechanism by which CBZ exerts an anti-inflammatory effect[19,64].

Rao et al[65] examined the effects of chronic CBZ treatment on rat brain inflammation. They found that CBZ had no effect on NF-κB in rat frontal cortex. To the best of our knowledge, the effect of CBZ on NF-κB has not been directly tested in other studies. On the other hand, the effects of CBZ on levels of inflammatory mediators that activate NF-κB have been tested in different *in vitro* and *in vivo* studies[66-71] – such studies may hint at a possible effect of CBZ on NF-κB. For example, CBZ was found to diminish nitric oxide (NO) and PGE2 production in LPS-stimulated rat glia cells[67]. Dambach et al[68] examined the effects of several antiepileptic drugs (AEDs) on inflammation in mixed primary astroglia/microglia cultures. They observed that CBZ had the most potent anti-inflammatory effect among the tested drugs. Himmerich et al[72] tested the effects of different AED including CBZ on cytokines production in a whole blood assay that was stimulated with the toxic shock syndrome toxin (TSST-1). They showed that CBZ inhibited IL-1β, IL-2 and TNF-α production while increasing IL-22 levels and had no effect on IL-4, IL-6 and IL-17 levels. Despite the results attesting for anti-inflammatory effects of CBZ, other studies have reported opposite results[73-75]. For example, Verrotti et al[73] investigated the effects of AEDs on blood levels of different cytokines in epileptic children. They found that CBZ increased the levels of IL-1, IL-1β, IL-6, IL-2 and monocyte chemoattractant protein-1[73].

In summary, there is a scarce of data regarding the direct effect of CBZ on NF-κB. However, some evidence suggests that CBZ has anti-inflammatory effects which may hint that it also inhibits NF-κB activity.

Lamotrigine

Lamotrigine (LTG) is an anticonvulsant drug also used for the treatment of depressive bipolar patients[76]. The anticonvulsant effects of LTG are attributed to its ability to inhibit the release of glutamate and aspartate from presynaptic membranes in several brain areas[77] and to block voltage dependent ion channels[78]. Similar to CBZ, the effect of LTG on NF-κB has not been directly tested. However, its effects on cytokines that are known to activate NF-κB could suggest for the existence of such effect. For example, it was found that LTG reduced IL-2, TNF-α and IL-1β production in whole blood assay taken from healthy subjects that was stimulated with TSST-1[72]. In a subsequent study, the same investigators showed that LTG significantly reduced IL-1β,

IL-2, IL-4, IL-6, IL-17 levels but did not affect IL-22 and TNF-α[79]. Furthermore, chronic LTG treatment led to a dose-dependent increase in viability of rat primary neuronal cerebellar granule cells[80]. This neuroprotective effect was attributed to inhibition of HDAC and marked increase in B-cell lymphoma-2 (Bcl-2) levels by LTG[80]. The latter is an apoptotic factor whose synthesis is controlled by NF-κB[81]. Similar results were obtained when chronic administration of LTG (or CBZ) significantly increased Bcl-2 levels in rat frontal cortex[82].

Antidepressants.

Antidepressant drugs are used for the treatment of depressive disorders[83] but are also given to patients suffering from anxiety disorders[84]. The precise mechanism of action of these drugs in the treatment of depressive disorders is not fully understood. One of the major hypotheses for their therapeutic mechanism is that they alter (increase) serotonin and/or norepinephrine levels in brain synaptic clefts[85]. However, other theories have also been suggested[85]. It is a diverse group of medications which includes several drug families including tricyclic antidepressants (TCAs), mono amine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), among others.

Imipramine

Imipramine (IMP) is a TCA antidepressant commonly used as a treatment for depressive and anxiety disorders. Few studies tested the effects of IMP on NF-κB revealing potent NF-κB inhibitory and anti-inflammatory effects. For example, the effects of IMP and clomipramine (another TCA) on NF-κB were examined in LPS-stimulated murine microglia and astrocytes[86]. Both IMP and clomipramine significantly inhibited IκB degradation and nuclear translocation of p65, which was accompanied by a marked decrease in TNF-α and IL-1β levels[86]. Similarly, treatment with IMP suppressed the expression of p65 and reduced its nuclear translocation in rat primary astrocytes[87]. Moreover, pretreatment with IMP decreased NF-κB DNA binding activity in the lung of LPS-treated mice[88].

Fluoxetine

Fluoxetine (FLX) is a SSRI widely used for the treatment of depressive and anxiety disorders. A number of studies examined the effects of FLX on NF-κB reporting inconsistent results. Bartholomä et al[89], showed that FLX (as well as the TCAs amitriptyline and desipramine) increased the transcriptional activity of NF-κB in hippocampal neurons and pheochromocytoma cells. Similarly, FLX was found to induce activation of NF-κB in human epithelial ovarian cancer cell lines, as it was seen in increased cytosolic p-IκBα and nuclear p65 levels[90]. On the other hand, Battaglino et al[91] found that FLX decreased NF-κB activity in osteoclast precursor cells. Similarly, Lim et al[92] have shown that FLX dose-dependently reduced NF-κB activity in brain of rats that were subjected to cerebral ischemia through middle cerebral artery occlusion. They also found that FLX attenuated NF-κB activity in LPS-stimulated primary microglia and neutrophil cultures[92]. Fluoxetine was found to inhibit NF-κB activity in LPS-treated rat primary neuron-glia cultures, as it was seen in a reduction in levels of phosphorylated IKKβ (p-IKKβ), p-IκBα and p-p65[93]. Moreover, FLX and the TCA amitriptyline were shown to inhibit nuclear translocation of NF-κB and decrease p65 nuclear levels in a transgenic mouse model of multiple system atrophy[94].

Other Antidepressants

Mirtazapine is an antidepressant with a complex mechanism of action. It blocks several neurotransmitter receptors (such as α2 and 5-HT$_{1A}$), among other functions. Zhu et al[95] reported that repeated mirtazapine administration reduced brain NF-κB activity in a rat model of neuropathic pain. The decrease in NF-κB activity was accompanied by a reduction in IL-1β and TNF-α levels and an elevation in IL-10 levels[95]. Similarly, desipramine was found to suppress NF-κB activity and diminish the levels of IL-1β and TNF-α in rat brain[96]. Moreover, the effects of tianeptine on the NF-κB complex were determined in human astroglial cells[97]. Tianeptine inhibited degradation and increased levels of IκBα, and reduced transcriptional activity of NF-κB[97]. Garabadu et al[98] reported that the SSRI citalopram reduced NF-κB levels in hippocampus and amygdala of rats that were subjected to cold restraint stress. In contrast, co-administration of amitriptyline with morphine in rats increased p-IκBα levels and increased translocation of p65 to the nucleus[99]. Moreover, the MAO inhibitor phenelzine was shown to enhance IκBα phosphorylation and increase nuclear translocation of NF-κB in LPS-treated microglia cells[100]. These

effects were accompanied by an increase in TNF-α and IL-6 production in the LPS-treated cells[100]. The SSRI paroxetine did not alter p-p65 levels and NF-κB activity in primary microglial cells[101].

Taken together, the summarized data suggest that different antidepressants (under different experimental conditions) inhibit the activity of NF-κB. However, other studies showed that some antidepressants do not alter or even increase NF-κB activity.

Antipsychotics

Antipsychotic drugs are the core of the pharmacotherapy for schizophrenia[102,103]. The therapeutic mechanism of antipsychotic drugs is associated mainly with their ability to block dopamine receptors in the brain[102,103]. Antipsychotic drugs affect other neurotransmitter (*e.g.,* serotonin) receptors and cellular pathways which are beyond the scope of this paper. Similar to other psychotropic drugs, antipsychotics also exert anti-inflammatory effects[104].

Haloperidol

Haloperidol (HPL) is a classic (typical) antipsychotic. A number of studies examined its effects on NF-κB. Bishnoi et al[105] treated rats with HPL for 21 days and examined its effects on nuclear p65 levels in the striatum. They found that HPL significantly increased p65 levels, which was accompanied by a significant increase in striatal TNF-α levels[105,106]. In another study, these authors showed that the effect of HPL on nuclear p65 in rat brain was dose-dependent – at 1 mg/kg it did not alter p65 levels while at 2 and 5 mg/kg it led to a significant increase in nuclear p65 levels[107]. Moreover, HPL was found to enhance DNA binding and transcriptional activity of NF-κB in mouse hippocampal HT22 cells[108]. Similar results were obtained by the same investigators when they examined the effects of HPL *in vivo* – HPL enhanced IκB phosphorylation and increased DNA binding activity of NF-κB in rat brain[109]. Sárvári et al[110] examined the effects of HPL on NF-κB in primary human adipose-derived stem cells taken from patients that were treated with different antipsychotic drugs. They observed a significant increase in gene expression of NF-κB1 and its target genes TNF-α, IL-1β, IL-8 and MCP-1 in cells that were taken from HPL-treated patients[110]. Other studies that examined the effects of HPL on NF-κB showed opposite results; namely, that HPL decreases NF-κB activity and/or levels[111,112]. For example,

chronic administration of HPL to rats decreased p50 levels, while p65 levels did not change in the nigral region of the brain[112]. Moreover, HPL was found to inhibit NF-κB activation in Jurkat T-cells[113]. Haloperidol decreased nuclear p65 levels and reduced NF-κB transactivation[113]. The summarized data indicate that the effects of HPL on NF-κB levels/activity vary in different studies and seem to be related to the experimental conditions and model system under which the drug was tested.

Other Antipsychotics

Chronic treatment with risperidone or clozapine (both are atypical antipsychotics) for 21 days in rats did not alter nuclear p65 levels in the striatum[105,106]. Similarly, risperidone and clozapine did not affect p65 levels and NF-κB transactivation in Jurkat T-cells[113]. On the other hand, treatment with risperidone was found to enhance NF-κB activity in mouse frontal cortex[111]. Moreover, chronic treatment with clozapine decreased p50 and p65 levels in the nigral region of rat brain[112]. Olanzapine is another atypical (second-generation) antipsychotic. The data regarding its effects on NF-κB is also not conclusive. For example, olanzapine and other antipsychotic drugs (including risperidone, clozapine, ziprasidone, quetiapine and aripiprazole) significantly increased gene expression of NF-κB1 and a number of its target genes in primary human adipose-derived stem cells[110]. Contrastingly, in a transgenic mouse model of multiple system atrophy olanzapine was found to reduce nuclear levels of p65[94]. Furthermore, the typical antipsychotic spiperone was shown to inhibit NF-κB activity in LPS-stimulated BV-2 microglia cells[114]. It inhibited IκB degradation and reduced nuclear levels and DNA binding of p65[114].

Conclusions

The reviewed data suggest that different psychotropic drugs influence the NF-κB complex differently. The discrepancy in the results of different studies (even for a particular drug) seems to derive from the various experimental conditions and model systems under which the drugs were tested. Nevertheless, a large body of evidence attests for a NF-κB inhibitory and anti-inflammatory effects of psychotropic drugs. The NF-κB inhibitory effect of psychotropic drugs is supported by the demonstration of a prominent

reduction in levels of pro-inflammatory media-
tors in different experimental models. Psy-
chotropic drugs were shown to influence NF-κB
at different levels of the pathway: (1) IKK phos-
phorylation; (2) IκB phosphorylation and/or
degradation; (3) phosphorylation and transloca-
tion of p65 (or another subunit) to the nucleus;
and, (4) binding of NF-κB to the DNA and its
transcriptional activation. Despite the observa-
tions above, other studies have shown that psy-
chotropic drugs do not affect or even increase
NF-κB activity. Such results have to be kept in
mind in order to avoid a premature closure on in-
hibition of NF-κB as a major mechanism by
which psychotropic drugs exert their anti-inflam-
matory effects.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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