neuroglia

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Perspective

The Role of Lactylation in Mental Illness: Emphasis on Microglia

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Abstract: A paradigm shift is currently taking place in the etiopathogenesis of neuropsychiatric disorders as immunometabolism is replacing the earlier neurotransmitter model. According to the new concept, cellular bioenergetics drives information processing in the central nervous system; therefore, neuropathology is conceptualized as a direct consequence of impaired metabolism. Along the same lines, endoplasmic reticulum stress and gut barrier dysfunction are emerging as novel targets in schizophrenia and affective disorders, linking immune responses to cellular distress. Furthermore, microglia, the brain's innate immune cells, acquire energy through oxidative phosphorylation, while in the resting state, and glycolysis upon activation, contributing to lactate accumulation and reduced brain pH. The same metabolic signature characterizes neuropsychiatric disorders as the central nervous system derives adenosine triphosphate from aerobic glycolysis, upregulating lactate and generating an acidic environment. Although known for over three decades, the link between dysmetabolism and neuropathology was poorly defined until the discovery of brain-resident innate lymphoid cells, including natural killer cells, and lactylation of histone and nonhistone proteins. In this perspective article, we examine three anti-inflammatory microglial systems relevant for neuropsychiatry: lactate, oxytocin, and the aryl hydrocarbon receptor. We also discuss potential interventions for restoring microglial homeostasis.

Keywords: microglia; neuropathology; lactylation; oxytocin; aryl hydrocarbon receptor

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1. Introduction

Severe neuropsychiatric illnesses, including schizophrenia and affective disorders, have been associated with brain metabolic disturbances, including excessive aerobic glycolysis and upregulated lactate, emphasizing that in the central nervous system (CNS) bioenergetics and information processing are highly intertwined [1–4]. Aerobic glycolysis and upregulated lactate, known as the Warburg effect, are the preferred energy sources of cancer cells and likely drive the pathogenesis of neuropsychiatric disorders [5,6]. Although low levels of lactate are neuroprotective, in excess it was demonstrated to induce neuronal apoptosis and decreased glutamatergic and GABAergic neurotransmission, hallmarks of neuropathology [7,8]. Along this line, a novel schizophrenia (SCZ) study has found that oral flora-derived lactate crosses the blood–brain barrier (BBB), generating CNS acidity [9,10].

Microglia are the CNS-resident macrophages known for vigilantly scanning the brain parenchyma, searching for tissue damage, molecular debris, and invading pathogens [10,11]. When changes are detected, microglia become activated and bioenergetically dependent on lactate [10]. Inflamed microglia, a characteristic of several neuropsychiatric disorders,

release proinflammatory cytokines and adopt a neurotoxic phenotype [12]. Hence, targeting microglial lactate is an emerging immunometabolic strategy in neuropsychiatric disorders [13–15] (see the section on Potential Therapeutic Strategies).

Recent studies have revealed that lactate is an essential CNS metabolite which promotes synaptic plasticity and exerts anti-inflammatory, antipsychotic, and antidepressant properties [16–20]. These are mediated by suppression of nuclear factor kappa B (NF-κB) via lactate signaling with its receptor hydroxycarboxylic acid receptor 1 (HCAR1) (also known as G-protein-coupled receptor 81 (GPR81)) [18]. In addition, lactate promotes axonal myelination as well as the rehabilitation of injured oligodendrocytes (OLs), highlighting a potential treatment modality for multiple sclerosis (MS) [21–23].

Lactylation is a post-translational modification (PTM) which utilizes lactate as a substrate; therefore, excessive availability of this metabolite promotes lactylation-mediated pathologies, including malignant transformation, Alzheimer's disease (AD), and neuropsychiatric disorders [24–27]. Lysine lactylation (Kla), discovered in 2019 by Yingming Zhao, can be a physiological or pathological process, depending on the lactylation levels, which regulates gene transcription by metabolically reprograming the neurons and glia [28,29] (Figure 1). In addition, the lactylation of nonhistone proteins, such as the high-mobility group box 1 (HMGB1), hypoxia-inducible factor 1 alpha (HIF-1α), and the membrane-organizing extension spike protein (moesin), was associated with tumorigenesis and schizophrenia, further linking dysfunctional lactylation to various pathologies [30–32].

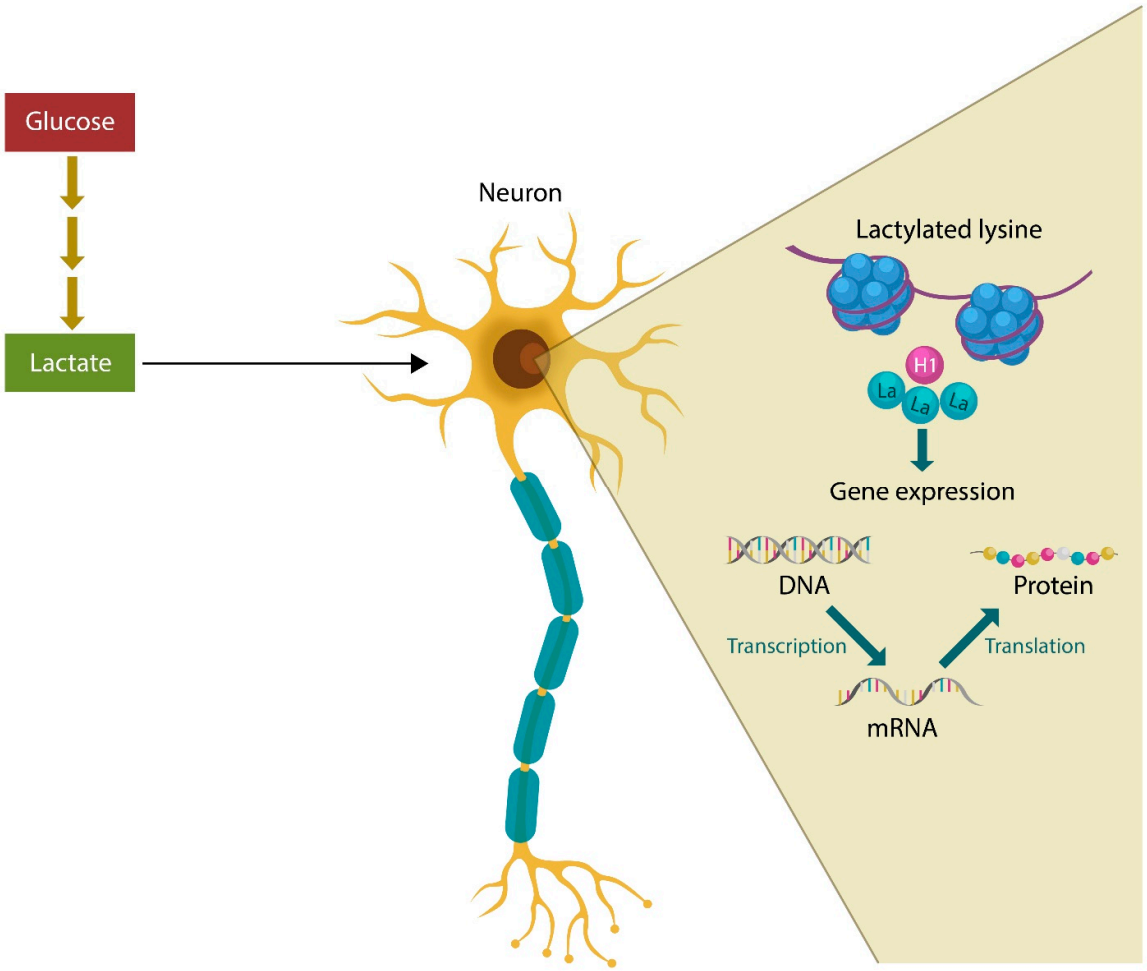

Figure 1. Excessive lactate derived from glucose metabolism can lead to excessive histone lysine lactylation (Kla), promoting pathologies, such as cancer, AD, schizophrenia, and related neuropsychiatric illnesses. Histone lactylation alters gene expression that in return affects translation and protein synthesis.

Another major discovery took place in 2022, when a subpopulation of oxytocin (OXT)-producing microglia was discovered, revealing a novel anti-inflammatory phenotype of these cells, likely distinct from the resting state [33,34]. Indeed, OXT signaling with OXT receptors (OXTRs), expressed on microglia, astrocytes, and oligodendrocytes, was reported to lower not only neuroinflammation but also depression, suicidal behavior, and psychosis, highlighting new potential pharmacological targets [35–44]. In addition, OXT promotes myelination and supports the nervous system white matter, likely explaining the reason this hormone was patented as an MS treatment (US patent 3274060A) [38,45,46].

The aryl hydrocarbon receptor (AhR), a cytosolic ligand-activated transcription factor, regulates the expression of numerous genes, including those involved in the response to environmental pollutants, polarization of microglia, myelination, and inflammation [47–49]. In the CNS, AhR exerts anti-inflammatory properties on microglia and astrocytes, promoting restorative neurogenesis and post-insult tissue regeneration [50]. However, in ischemic strokes, AhR may activate microglia, triggering inflammation, suggesting that this receptor is not only tissue-specific but also dependent on the pathology type [51]. In addition, AhR modulates meningeal innate lymphoid cells (ILCs), especially the protective CD56bright natural killer cells (NKCs), promoting a tolerant, IL-10-generating phenotype [52,53]. Conversely, dysfunctional NKCs promote neuroinflammation by aberrantly eliminating the anti-inflammatory resting microglia, disrupting immune homeostasis by selectively sparing the activated, inflamed cells [54].

In this perspective article, we take a closer look at three anti-inflammatory microglial systems relevant for neuropsychiatry, lactate, OXT, and AhR, as well as potential interventions for restoring microglial homeostasis.

2. Lactate and Mental Illness

Major neuropsychiatric illnesses, including schizophrenia and affective disorders, have been associated with decreased brain pH, lactic acid accumulation and upregulated glycolysis [1,2,8]. From a bioenergetic perspective, the brain cells of mentally ill individuals resemble cancer cells, as adenosine triphosphate (ATP) is acquired through aerobic glycolysis, or the Warburg effect, decreasing the brain pH, while oxidative phosphorylation (OXPHOS) is downregulated.

Lactate plays a key role in the CNS where it functions as a metabolite as well as a neurotransmitter. Lactate is endowed with anti-inflammatory properties as it inhibits NK-kB, promotes myelination, and regulates microglial function [22,55]. Indeed, microglia possess the molecular machinery to shift metabolism according to phenotype; resting microglia rely on OXPHOS, while activated microglia utilize aerobic glycolysis [23].

Innate lymphoid cells (ILCs) signaling with microglia and the discovery of histone and nonhistone proteins lactylation have contributed to a better understanding of the role of aerobic glycolysis in neuropsychiatric disorders. Although lactate is neuroprotective and mediates synaptic plasticity, excessive lactylation can alter neuronal function, shifting them to an energy state akin to malignant cells [56–58] (see section Microglia, lactylation and mental illness). For example, aberrant neuronal cell cycle reentry and aneuploidy have been observed in patients with SCZ, suggesting that lactate triggers "reprimitivization" of brain cells or the acquisition of stem cell properties [30,59–63]. This is further substantiated by the neuronal progenitor cells' dependency on aerobic glycolysis, suggesting that local acidity promotes undifferentiated cellular phenotypes [64,65]. Indeed, in an acidic environment, somatic mammalian cells could be epigenetically reprogrammed into pluripotent stem cells, while L-lactate has been shown to induce neurogenesis in adult hippocampal neurons [66–68]. Moreover, exposed to lactate, cardiomyocytes were demonstrated to reenter the cell cycle in a manner reminiscent of neurons, emphasizing the link between low pH and postmitotic cells' replication attempts [69].

Moesin is a member of the ezrin-radixin-moesin (ERM) family of proteins which are constituent parts of the cellular cytoskeleton, and thus implicated in mitosis [70]. In AD, moesin activates neuronal cell cycle reentry, indicating that lactylation of this protein

may promote neuropsychiatric pathology [71–73]. Indeed, moesin was implicated in schizophrenia and plays a major role in the aberrant NKCs activation [74–76] (Figure 2).

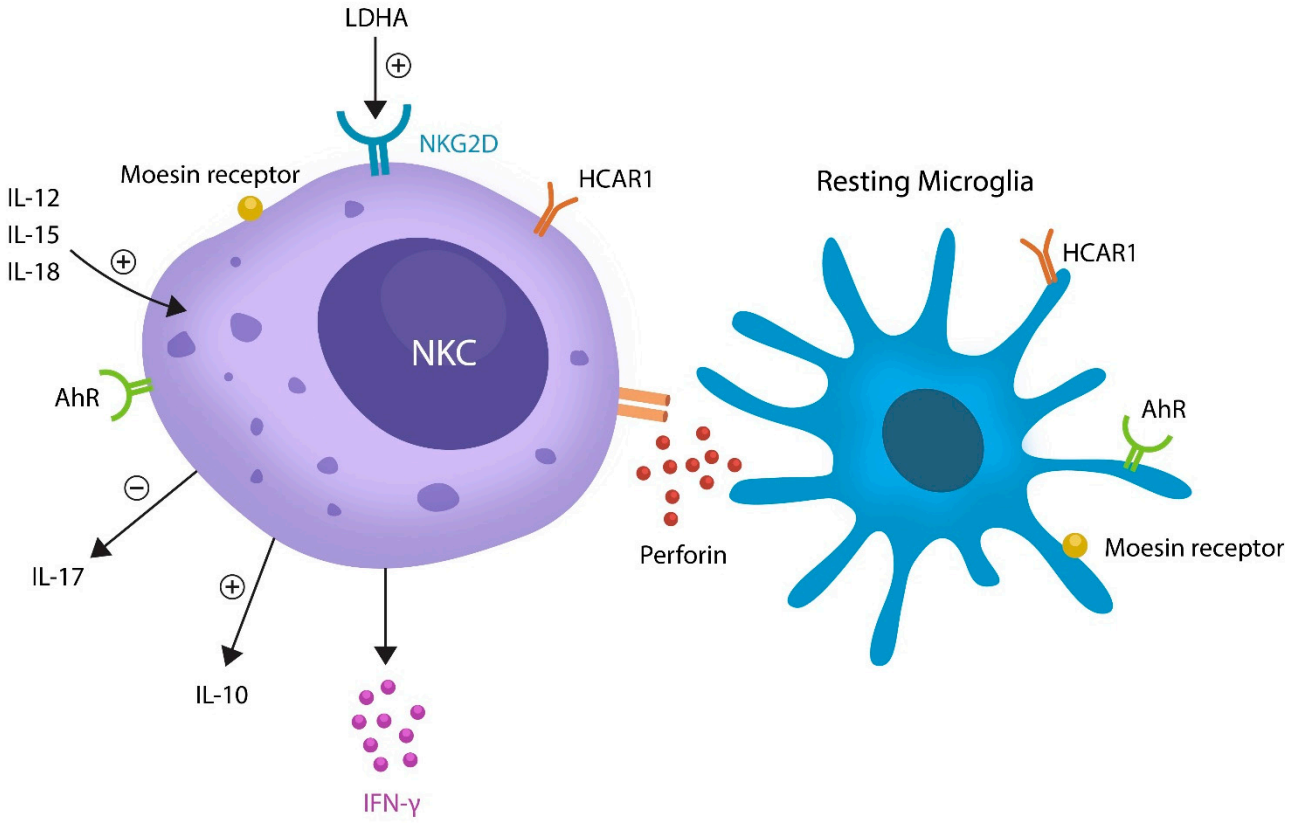

Figure 2. Aberrant elimination of resting microglia by lactate-activated NKCs. LDHA or LDH-5 can activate NKC via NKG2D receptors. IL-12, IL-15, and IL-18 activate NKCs, facilitating the release of IL-10, IL17, and IFN-γ. NKCs express HCAR1, AhR, and moesin receptors, proteins previously implicated in neuropathology. Activated NKCs release perforin, a toxic molecule known for eliminating resting microglia. Because activated microglia are not killed, this is a likely mechanism of tilting the balance toward inflammation.

Histone Kla, a reversible PTM, is regulated by EP300 and class I histone deacetylases (HDAC1–3), enzymes which add and remove lactate to and from the histone proteins [77–79]. Both HDAC1–3 and EP300 have been implicated in SCZ and/or the adverse effects of antipsychotic drugs via the brain-derived neurotrophic factor (BDNF) [80–82]. As BDNF gene histone modifications contribute to fear extinction, this system's malfunction likely triggers Kla-mediated neuropsychiatric symptoms, such as excitation, social defeat, anxiety, and stress [83,84]. Interestingly, the neuroprotective properties of BDNF consist of preventing neuronal cell cycle reentry, further linking attempted mitosis to psychopathology [85].

NKCs are members of ILCs which are activated by lactate and sense pathological changes, migrating to the affected sites, including the brain parenchyma [86]. Lactate-activated NKCs were found to eliminate resting microglia but not the activated phenotype, suggesting that the pathological loss of anti-inflammatory microglia triggers neuroinflammation and the related pathology [54] (Figure 2). Moreover, as activated microglia have been linked to neurotoxicity and demyelination, pathological NKCs may predispose to autoimmune inflammation, including multiple sclerosis (MS) [12,87,88]. This is significant as impaired NKCs were found in the first episode of SCZ in antipsychotic-naïve individuals, suggesting that manipulation of these cells could ameliorate psychotic symptoms [89].

Recent studies have revealed an alternative source of brain lactate, the microbial community residing in various body compartments, including the oral cavity and the GI tract [1,9]. Indeed, the high lactate producers *Bifidobacterium* and *Lactobacillus* spp. have been shown to maintain the integrity of intestinal epithelial cells (IECs) and the survival of other commensals [90,91]. However, excessive lactate accumulation in the GI tract can trigger pathology by lowering the production of short-chain fatty acids (SCFA), biomolecules in charge of numerous CNS and peripheral physiological functions [92]. Indeed, the lactate-induced anti-inflammatory and immunosuppressive milieu can predispose to cancer as well as microbial and viral infections [93–95]. For example, lactate signaling with microglial HCAR1 promotes tissue regeneration and healing; however, it may also induce pathology by suppressing the phagocytosis of malignant or pathogen-infected cells [94–96].

Mental Illness, Lactylation, and Microbes

Histone Kla is not limited to mammals as it was also demonstrated in prokaryotes, linking microbial lactate to host neuropathology [97]. For example, *Escherichia coli (E. coli*) proteins YiaC and CobB induce histone lactylation, likely explaining the association of this bacterium with schizophrenia [98]. This was exemplified in the 2011 outbreak of *E. coli* in Germany which was accompanied by psychosis, linking this pathogen to mental illness [99,100]. In another example, urinary tract infection (UTI), caused primarily by *E. coli*, is known for the potential to trigger new-onset psychosis or the exacerbation of psychotic symptoms in stable patients with schizophrenia, further illustrating the link between this pathogen and mental illness [101,102].

Lactylation of nonhistone proteins, HMGB1, HIF-1α, and moesin, was associated with both schizophrenia and *E. coli* infection, linking this microbe once more to neuropathology [30,31,103–106]. Moreover, *Toxoplasma gondii*, an intracellular protozoan, previously associated with SCZ, is another example of pathogen-mediated lactylation, causing host neuropathology [107]. Indeed, a recent study found that *Toxoplasma gondii*, containing 523 lactylated proteins, eliminates host inhibitory synapses by aberrantly activating microglia [108,109]. Moreover, *Toxoplasma gondii* was demonstrated to induce endoplasmic reticulum (ER) stress as well as intestinal barrier disruption, pathologies associated with mental illness [110,111].

Taken together, lactate is a CNS protective metabolite that not only contributes to energy metabolism and signaling but also serves as a substrate for lactylation. Excessive lactate accumulation from local metabolism or the microbiome may trigger lactylation-associated pathology, such as cancer, AD, or neuropsychiatric illness.

3. Oxytocin and Microglia in Mental Illness

Oxytocin (OXT)-oxytocin receptor (OXTR) signaling comprises a microglial anti-inflammatory pathway. OXT is a neuropeptide synthesized in the hypothalamus and stored in the posterior pituitary prior to being released into the systemic circulation. OXT is both a hormone and a neurotransmitter, the former mediating parturition and lactation, while the latter affects social behavior, affiliation, intimacy, and mother–infant bonding [112]. A recent study found that the OXT concentration in the brain can reach levels 1000 times higher than in the systemic circulation, highlighting the importance of this biomolecule for CNS function [113].

Low blood OXT levels were reported in patients with SCZ marked by negative symptoms, while intranasal administration of OXT was shown to ameliorate this condition [114,115]. Indeed, like lactate, OXT modulates synaptic plasticity and upregulates adult hippocampal neurogenesis, enhancing long-term potentiation and memory, properties that likely mediate this hormone's antipsychotic and antidepressant properties [116–118].

OXT decreases microglial inflammation by lowering ER stress via translation initiation factor 2 alpha/transcription factor ATF4 (eIF-2α–ATF4), a common autophagic pathway disrupted in SCZ and major depressive disorder (MDD) [119–121]. For example, eIF-2α–ATF4 lowers ER stress by upregulating Sigma-1 receptors (Sig-1Rs), proteins involved in

several neuropsychiatric disorders. Indeed, several antidepressant and antipsychotic drugs, including fluvoxamine, sertraline, and haloperidol, lower ER stress, suggesting that the therapeutic properties of these agents could be mediated by eIF-2α–ATF4 [122,123]. Aside from lowering ER stress, Sig-1Rs protect the intestinal barrier and BBB, linking eIF-2α–ATF4 to microbial translocation [124,125]. It stands to reason, therefore, that strengthening the gut barrier and lowering ER stress in intestinal epithelial cells (IECs) are emerging strategies for neuropsychiatric disorders (Table 1) (clinical trials identifier NCT03183609) [126–131]).

Table 1. The action mechanisms of Lactate, OXT, and AhR.

Lactate	OXT	AhR	References
Deactivates microglia by NF-kB inhibition	Deactivates microglia via eIF-2α–ATF4 pathway	Deactivates microglia via NF-kB	[4,15,50]
Excess lactate promotes Kla	No known effect on lactylation	Increases LDHA and lactate	[24,132]
Lowers ER stress	Lowers ER stress	Lowers ER stress	[16,33,133]
Augments gut barrier function	Augments gut barrier	Augments gut barrier	[90,124,134]
Upregulated in schizophrenia	Downregulated in schizophrenia	Implicated in schizophrenia	[1,135,136]

Several studies have connected OXT with the selective serotonin reuptake inhibitors (SSRIs), emphasizing that this hormone may contribute, at least in part, to the action mechanism of antidepressant drugs [137,138]. Moreover, sexual dysfunction, a common SSRI adverse effect, was associated with decreased OXT blood levels, linking this hormone further to the serotonergic system [139,140]. This is significant as OXT exerts antidepressant properties of its own and may be indicated in situations when other antidepressants are to be avoided, such as during pregnancy and the postpartum period as well as in patients with sexual dysfunction.

Aside from the antidepressant action, OXT exerts antipsychotic properties, documented as early as the 1970s and 1980s, followed by clinical trials of intranasal OXT in 2010, studies which have produced encouraging results for schizophrenia patients [35,135,141] (clinical trials identifier NCT01621737).

In 2022, it was discovered that a subpopulation of microglial cells is capable of generating OXT, drawing the attention of researchers and clinicians to the anti-inflammatory properties of these cells [33,34]. Indeed, OXT signaling with OXTR, expressed on microglia, astrocytes, and oligodendrocytes, lowers neuroinflammation, depression, suicidal behavior, and psychosis, indicating that OXT signaling is a significant neuropsychiatric target [35–44] (see section Microglia, lactylation and mental illness).

Taken together, OXT and lactate exert antipsychotic and antidepressant properties through different mechanisms. Impaired OXT signaling may trigger neuropathology by increasing ER stress in IECs, disrupting the GI tract barrier.

4. Aryl Hydrocarbon Receptor and Mental Illness

ILCs are mucosa-anchored lymphocytes which express transcription factors instead of T- or B-cell receptors; they are activated by specific cytokines and generate their own cytokine output. ILCs, comprised of NKCs, ILCs types 1, 2, 3, and regulatory ILCs (ILCreg), are situated at the biological barriers, including the gut and meninges [142,143]. Human ILCs express AhR which is abundantly represented on CD56bright NKC, emphasizing further the protective role of these lymphocytes [53,144]. Glycolytic enzymes, lactate dehydrogenase A (LDHA) or lactate dehydrogenase-5 (LDH-5), activate NKG2D receptors, regulating CD56bright NKC responses, suggesting that excessive lactate likely disrupts the function of these lymphocytes [144,145].

Aside from AhR and lactate, NKCs, including CD56bright, are activated by IL-12, IL-15, and IL-18, releasing interferon γ (IFN-γ) and IL-10 (Figure 2) [1–4]. In addition, AhR lowers the proinflammatory IL-17 previously implicated in both SCZ and MS [146–148].

Moreover, dysfunctional IL-12, IL-15, IL-18, IFN-γ, and IL-10 have been associated with schizophrenia, highlighting further the key role NKCs in this pathology [149,150]. AhR also suppresses microglial and astrocytic inflammation, switching these cells from inflammatory to the restorative phenotype [51,151,152].

Aberrant elimination of resting microglia by NKCs is likely the root cause of neuroinflammation, documented in many neuropsychiatric disorders; therefore, rescuing these cells should be explored as a therapeutic strategy [53,54]. For example, the expansion of circulating CD56bright NKCs has been associated with improved MS symptoms, suggesting that these cells may also play a beneficial role in SCZ and affective disorders [153,154]. Indeed, a low CD56 lymphocyte count was demonstrated in antipsychotic-naïve patients with schizophrenia, and it was upregulated by treatment, emphasizing the beneficial properties of these cells [134] (for the role of AhR in microglial cells, see the section Microglia, lactylation and mental illness). As CD56bright NKCs express AhR, the clinical symptoms may respond to the pharmacological manipulation of this receptor [155] (discussed in the section on Potential Therapeutic Strategies).

In the gut, AhR protects the intestinal barrier by binding microbiota-derived metabolites as well as the SCFAs, linking dysfunctional AhR signaling to gut barrier disruption and microbial translocation [156,157].

Novel studies have shown that AhR functions in a tissue-specific manner, dependent on the ligand affinity, likely accounting for the variable, often opposite, responses elicited in one organ vs. another [158,159]. For example, endogenous AhR ligands, such as tryptophan and microbial metabolites, may exacerbate breast cancer while exerting salutary effects in colorectal carcinoma [132,160–163]. Moreover, in the gut, AhR enhances the barrier function while inducing liver toxicity, illustrating the difficulties encountered in trying to develop AhR therapeutics. Having said that, selective modulators, such as flavonoids and isoflavones, may offer a solution [164–167] (Table 2) (see the section on potential interventions).

Table 2. Potential interventions for restoring the homeostasis of anti-inflammatory microglia.

Lactate	OXT	AhR	References
L-lactate	Intranasal OXT	Flavonoids	[114,168,169]
Lactylation inhibitors	ARBs	Nattokinase	[169–171]
Demethylzeylasteral (DML)	ISRIB	Isoflavones	[172–174]
Sirtuins	PAK inhibitors	Laquinimod	[170,175,176]
Sodium oxamate	MIF-1	CH 22391	[177–179]
Gallnut extract CN102836354A	OT-1 (TC OT 39)	Triptans (Sumatriptan)	[180–182]
Galloflavin (NSC 107022)	WAY 267464	CD56bright NKCs	[183–185]

AhR promotes myelination and lowers ER stress, suggesting that MS, MDD, schizophrenia, and bipolar disorder may be exacerbated by the dysfunction of this protein [133,186]. Interestingly, carbidopa and the unique antipsychotic drug clozapine are AhR agonists, linking this receptor to the dopaminergic system and probably explaining both the efficacy as well as the side effects of these agents [187,188]. Moreover, dopamine is an AhR ligand, further implicating this receptor in mental illness [136]. Indeed, AhR was implicated in schizophrenia by the earlier studies, emphasizing a novel psychopharmacological target [189]. In a rodent model, clozapine attenuates experimental autoimmune encephalomyelitis (EAE), suggesting that the unique anti-suicide properties of this drug (not shared with other antipsychotic agents) may be mediated by AhR [190]. Yet another study saw that agranulocytosis, an autoimmune-like adverse effect of clozapine, was associated with DRB1*15:01, a rare human leukocyte antigen (HLA), and a major MS risk factor, linking agranulocytosis to this genetic marker [191,192].

Taken together, AhR exerts antidepressant and antipsychotic properties by several mechanisms: 1. microglial deactivation, 2. lowering ER stress, 3. enhancing the gut barrier, 4. upregulating lactate, and 5. myelination. These protective effects may explain the unique clozapine properties (Table 1).

5. Microbial Translocation Outside the GI Tract

In our previous work, we have discussed microbial translocation from the GI tract into the host systemic circulation, suggesting that the pathogenesis of several idiopathic diseases could be explained by the immune responses to extraintestinal microbial proteins [193]. As higher gut and BBB permeability markers, including the soluble form of CD14 (sCD14), were documented in neuropsychiatric illness, this pathology may, at least in part, result from microbial migration through the gut barrier [194–196].

Various antigens of GI tract microbes, including *Bacteroides*, *Bifidobacterium*, *Acinetobacter*, and *Pseudomonas*, have been shown to exhibit molecular mimicry with the host myelin basic protein (MBP), suggesting that autoantibodies against myelin, documented in MS, schizophrenia, and bipolar disorder, may be conventional immunoglobulins directed at the displaced microbes or their components [197–199]. In addition, as myelin contains a serotonin binding site, the autoantibodies against serotonin, found in MS and MDD, may be classical antibodies against serotonin-producing microbes, such as *Clostridia* or *staphylococci* [200,201]. Furthermore, bacterial N-acetylmuramyl dipeptide was reported to mimic myelin, likely triggering antibodies upon translocation into host tissues [202]. These findings are significant as they emphasize that strengthening the gut barrier to lower microbial migration likely comprises a novel therapeutic strategy in neuropsychiatric disorders. In fact, inflammation in response to translocated microbial proteins was previously associated with suicidal behavior, suggesting that gut barrier restoration should be instituted as a therapy in mental illness [203–205]. Indeed, some antidepressant drugs currently utilized in clinical practice were demonstrated to optimize the gut barrier function, suggesting an alternative, noncanonical, mechanism of action [206]. Microbial translocation across the gut barrier has been documented in MDD, suicidal behavior, bipolar disorder, aggression in SCZ, and neurodegeneration, suggesting that the loss of anti-inflammatory microglia plays a crucial role in neuropathology [196,202–205,207,208].

6. Potential Therapeutic Strategies

Lactate, OXT, and AhR are therapeutic targets rarely considered in the treatment of neuropsychiatric disorders; however, they play a major role in the CNS and immune metabolism.

7. Lactate

Novel studies have shown that peripheral administration of L-lactate exerts antidepressant effects by increasing hippocampal lactic acid which upregulates neurogenesis and inhibits microglial activation [168,209] (Table 2).

1. Lactylation inhibitors are compounds belonging to several classes of therapeutics, such as LDHA inhibitors, demethylzeylasteral (DML), and phytotherapeutics, including polyphenols. Here, we review only the agents that can cross the BBB, lower ER stress, and strengthen the intestinal barrier [210,211]. These are as follows.
2. Sirtuins

Studies in oncology have reported that sirtuins (SIRT), especially SIRT2, can remove lactate from the histone lysine, showing that de-lactylation may comprise a novel strategy for microglial depolarization, an approach likely beneficial in MDD and SCZ [170]. The effect of SIRT in these disorders has been documented by earlier research [212–214].

Demethylzeylasteral (DML) inhibits lactylation of histone H3, a protein associated with MDD, suggesting that it could exert antidepressant properties [172,215].

3. LDH inhibitors Lactate-HCAR1 signaling is regulated by LDHA or LDH-5, glycolytic enzymes upregulated by psychological stress, suggesting that inhibiting these en-

zymes could be therapeutic for neuropsychiatric illness [216]. LDH inhibitors, include the following:

3.1. Sodium oxamate, a structural analog of pyruvate, is known for lowering ER stress by promoting protective autophagy, properties beneficial for neuropsychiatric disorders [177,217]. To the best of our knowledge this compound has not been evaluated for psychiatric conditions.

3.2. Chinese Gallnut Extract from *Galla chinensis* is a traditional Chinese medicine and a potent LDHA inhibitor which was patented for the treatment of MDD and is currently in clinical trials (Chinese patent CN102836354A) (US patent 10098854B2) (clinical trials identifier NCT04080752) [180,218].

3.3. Galloflavin or NSC 107022 is a polyphenol found in berries which upregulates SIRT6, a key regulator of neuronal mitochondria [183,219]. Dysfunctional SIRT6 was associated with depression-like behavior in mice, suggesting potential benefits for humans with MDD [220]. Galloflavin has been patented as a modulator of protein kinases that can treat a variety of conditions, ranging from cancer to neuropsychiatric disorders (US patent 20030187007A1).

8. OXT

OXT signaling with OXTRs has been shown to inhibit activated microglia and increase the number of NKCs, a phenomenon documented in schizophrenia [221]. Recently, an OXT-generating microglial population was identified, suggesting that anti-inflammatory microglia may regulate many physiological functions that could cause pathology when disrupted [222,223].

8.1. Angiotensin IV (ANG IV) as an OXT Agonist

Several studies demonstrated that microglia express a functional renin-angiotensin system (RAS), including angiotensin II type 1 receptors (AT-1Rs) [224]. Conversely, AT-1R blockers (ARBs), especially the BBB-crossing candesartan, have been found therapeutic in schizophrenia and MDD, linking dysfunctional RAS to inflamed microglia [171]. This is significant as angiotensin II (ANG II) is a negative OXT regulator; thus, ARBs may not only depolarize these cells but also enhance OXT release [33,34,224,225]. Indeed, angiotensin IV was reported to upregulate OXT in vitro and in vivo, probably by inhibiting oxytocinase, the hydrolyzing enzyme of this hormone [226].

OXT inhibits eIF-2α–ATF4 signaling, a pathway implicated in ER stress, suggesting that the beneficial neuropsychiatric effects of OXT can likely be attributed to autophagy [44]. Indeed, the antiretroviral drug nelfinavir has been shown to promote ER stress by eIF2α phosphorylation; in contrast, the integrated stress response inhibitor (ISRIB), a protein with antidepressant and antipsychotic properties, inhibits nelfinavir-induced ER stress via eIF2α dephosphorylation [173]. The related drugs, p21-activated kinase (PAK) inhibitors, were found beneficial in SCZ, emphasizing new potential targets in this disorder [175]. IRIB was patented in Australia as a broad therapeutic agent that may be useful in pathologies involving learning, memory, immunity, intermediary metabolism, insulin production, and resistance to unfolded protein stress (Australian patent 2020229748A1).

8.2. OXT Fragments

OXT, comprised of nine amino acids, was found to retain biological properties even when cleaved in shorter segments. For example, melanocyte-inhibiting factor-1 (MIF-1), the N-terminal segment of oxytocin, possesses antidepressant and antipsychotic properties, suggesting that OXTR can be activated by related small ligands [178,227]. MIF-1 was patented for cancer, autoimmune diseases, fibrotic diseases, inflammation, and neurodegenerative diseases (international patent WO2009040045A2). Several OXT-like molecules have also been studied, including lipo-oxytocin-1 (LOT-1), a synthetic OXTR agonist (also known as TC OT 39), and WAY-267464, an OXTR agonist and vasopressin 1 receptor (V1AR) antagonist [181,184]. The efficacy of these ligands for neuropsychiatric disorders has not been

evaluated in clinical trials; however, several patents were obtained for use in neurological and psychiatric disorders (international patent WO2018107216A1) (EP2326341B1).

9. AhR

AhR binds diverse ligands derived from the environment, diet, microbes, and cellular metabolism, enabling cells to adapt to the changing exogenous or endogenous conditions. Drugs, chemicals, and plant-derived compounds, including isoflavones, attach with different affinities to AhR [228]. Nattokinase, a soybean fermented by *Bacillus subtilis var. natto,* contains AhR-binding flavonoids [169]. Indeed, several isoflavones, including, soybeans, genistein, daidzein, glycitein, formononetin, biochanin, and phytoestrogens, have been found to exert antidepressant and antipsychotic properties [174,229,230].

- Laquinimod, a quinolone-3-carboxamide developed for the treatment of MS, is a selective AhR ligand that demonstrated encouraging results in animal models of MDD and anxiety [176].
- CH223191 is an antagonistic selective AhR ligand with a favorable profile for neuropsychiatric disorders [179]. This compound was patented in the US for cancer treatment but has still to enter clinical trials for neuropsychiatric disorders (US patent 20160175278A1).
- Sumatriptan, a selective 5-hydroxy-triptamine (5-HT1) receptor agonist, activates human AhR, exerting anti-inflammatory properties, suggesting beneficial effects on activated microglia [182,231].
- Dimethyl fumarate, indicated for MS, is not an AhR ligand; however, it upregulates the protective AhR-expressing CD56bright NKCs which eliminate the detrimental autoreactive immune cells to avert autoimmunity [232,233]. For this reason, CD56bright NKCs expansion via AhR or transplantation may comprise a potential therapeutic strategy for neuropsychiatric illness. For example, CD56bright NK cells allogeneic or stem cell transplantation, a treatment used for acute myeloid leukemia, could be therapeutic in both MS and schizophrenia [185,234].

10. Microglia, Lactylation, and Mental Illness

Although microglia comprise less than 10% of the brain cells, it plays a major role in neuropsychiatric pathology [235]. Resting microglia are neuroprotective as evidenced by in vivo two-photon imaging of fluorescent-labeled neurons and microglia, demonstrating that these cells participate in the plasticity of neuronal circuits [236]. Resting microglia actively communicate with other brain cells, including astrocytes, neurons, and ILCs [237–239]. Recent studies have shown that microglia express monocarboxylate transporters (MCTs) and HCAR1, suggesting that lactate plays an important role in the reprograming of these cells [240,241]. Numerous studies have found that young and healthy brains rely on glycolysis and lactate, while aging brains lose glycolytic ability [242]. For example, dysfunctional glycolysis was associated with AD pathology as well as schizophrenia [243,244]. Excessive lactate generation contributes to lactylation of histone and nonhistone proteins, engendering pathology [245].

Microglia are brain resident macrophages that express OXT receptors, suggesting that these proteins contribute to anti-inflammatory microglia, a likely protection against mental illness [246,247].

Microglia express AhR, proteins involved in several pathologies, including glioblastoma [248]. AhR is a new receptor of interest in schizophrenia, not only because it binds dopamine but also because schizophrenia-associated exogenous toxins, such as plasticizers, are ligands at this receptor [249,250]. In addition, many protective metabolites synthesized by gut microbes, including indole and tryptophan, are AhR ligands, suggesting that the gut–brain axis likely operates through this receptor [251].

It has been reported that aberrantly activated microglia become neurotoxic and engage in the elimination of healthy neurons or synapses, a pathology involved in schizophrenia [252–254].

11. Limitations

Many compounds described above are phytotherapeutics, primarily natural products, such as sirtuins, or traditional foods, including nattokinase and the Chinese Gallnut Extract, that have been used by humans for hundreds of years. The ability of these molecules to act as AhR ligands suggests beneficial effects in neuropsychiatric illness, and clinical trials should be initiated to assess their efficacy. Likewise, the ability of sirtuins to remove histone lysine lactate has reawakened the interest in these compounds, previously studied for neurodegenerative disorders, as potential medical foods or dietary interventions.

Furthermore, several compounds mentioned above have been patented in different countries and some are currently in clinical trials, while others have not reached that stage yet. However, the profile of these agents, estimated by their action mechanism described in the patent application, suggests that they should be evaluated as antidepressant or antipsychotic agents. For example, dimethyl fumarate was patented in Europe for the treatment of MS; however, as this drug exerts neuroprotective as well as anti-inflammatory effects on astrocytes and microglia, it likely possesses antidepressant and antipsychotic properties which should be evaluated in clinical trials.

Additionally, we need to state that most of the pathophysiological mechanisms described in this article are newly elucidated. As the details become increasingly available, it would be much easier to prioritize different potential therapeutic targets. Moreover, understanding these mechanisms will eventually allow for an in-depth stratification of neuropsychiatric patients, and a move toward an improved precision medicine approach.

12. Conclusions

Increasing awareness of the shortcomings of the neurotransmitter paradigm contributed to the development of a new concept, metabolism-driven information processing. This model, illustrated by the previously known association of neuropsychiatric pathology with excessive aerobic glycolysis, was put in perspective by the discovery of ILCs and lactylation. The consequences of excessive brain lactate and increased local acidity include the following:

1. The aberrant elimination of anti-inflammatory resting microglia by pathologically activated NKCs.
2. The reactivation of the neuronal cell cycle with resultant aneuploidy or apoptosis as these cells lack the molecular machinery to complete mitosis.
3. Several interventions may restore the homeostasis of anti-inflammatory microglia, including 1. lowering lactylation, 2. enhancing OXT signaling, 3. modulating AhR, and 4. expanding CD56NKCs. These strategies lower the ER stress and strengthen the gut barrier, limiting microbial migration outside of the GI tract, thus decreasing the risk of microglial activation by translocated bacterial antigens.

More studies are needed to clarify the role of lactylation of histone and nonhistone proteins in mental illnesses and the interaction of lactylation with meningeal ILCs.

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Abbreviations

NF-κB = nuclear factor kappa B; HCAR1 = hydroxycarboxylic acid receptor 1; GPR81 = G-protein-coupled receptor 81; Kla = lysine lactylation; OXT = oxytocin; OXTRs = receptors; AhR = aryl hydrocarbon receptor; NKCs = natural killer cells; ERM = ezrin-radixin-moesin; HDAC1 = class I histone deacetylases; ILC = innate lymphoid cells; HMGB1 = high-mobility group box 1; HIF-1α = hypoxia-inducible factor 1α; BDNF = brain-derived neurotrophic factor; IEC = intestinal epithelial cells; SCFA = short-chain fatty acids; ISRIB = integrated stress response inhibitor; MIF-1 = melanocyte-inhibiting factor-1; OXPHOS = oxidative phosphorylation; V1AR = vasopressin 1 receptor; SCZ = schizophrenia.

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