Drug repositioning for treatment-resistant depression: insights from a pharmacogenomic study

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Abstract

About 20-30% of patients with major depressive disorder (MDD) develop treatment-resistant depression (TRD) and finding new effective treatments in these patients has been a challenge. This study aimed to identify new possible pharmacological options for TRD by comparing genes previously associated with this phenotype and known drug targets.

Genes associated with TRD were compared with those coding for targets of drugs in any phase of development, nutraceuticals, proteins and peptides from Drug repurposing Hub, Drug-Gene Interaction database and DrugBank database. We tested if known gene targets were enriched in TRD-associated genes by using a hypergeometric test. Compounds showing a significant enrichment in TRD-associated genes after false-discovery rate (FDR) correction were annotated and compared with those showing enrichment in genes associated with MDD in the last Psychiatric Genomics Consortium genome-wide association study.

Among a total of 12,686 compounds or classes, 612 were enriched in TRD-associated genes (FDR $p<0.05$). Significant results included drugs which are currently used in TRD (e.g. lithium and ketamine), confirming the rationale of this approach. Interesting molecules included modulators of inflammation, renin-angiotensin system, proliferator-activated receptor agonists, glycogen synthase kinase 3 beta inhibitors and the rho associated kinase inhibitor fasudil. Naturally occurring compounds, mostly antioxidant polyphenols, were also identified. Drugs showing enrichment for TRD-associated genes had a higher probability of enrichment for MDD-associated genes compared to those having no TRD-genes enrichment ($p<2.2e-16$).

This study identified new potential treatments for TRD using a *in silico* approach. Further testing of these results may lead to new treatments for TRD.

Keywords: treatment-resistant depression; drug repurposing; pharmacogenetics; major depression

1. Introduction

Between 20% and 30% of persons with major depressive disorder (MDD) develop treatment-resistant depression (TRD), a condition usually defined as lack of response to at least two different antidepressants (Souery et al., 1999) (Rizvi et al., 2014). TRD is associated with social and occupational impairment, suicidal thoughts, decline of physical health and increased health care utilization (Trivedi et al., 2006) (Souery et al., 2011). Annual costs for health care and lost productivity were estimated to be US$5,481 and $4,048 higher, respectively, for a patient with TRD versus a patient with treatment-responsive depression (Mrazek et al., 2014).

Finding new effective treatments in TRD has been a challenge. As a matter of fact, almost all the available antidepressants act through the modulation of monoamine reuptake and/or monoamine receptors and patients with TRD tend to respond poorly to these drugs (Harmer et al., 2017). The return to long known compounds with alternative mechanism of action but problematic side effects such as ketamine was chosen since other options with similar effectiveness are lacking (Harmer et al., 2017).

Traditional drug development is a long and expensive process: getting a drug to market currently takes 13-15 years and between US$2 billion and $3 billion on average, and the costs are going up, even though the number of drugs approved every year per dollar spent on development has remained flat or decreased for most of the past decade (Nosengo, 2016). Repurposing of existing drugs (approved or during development for any disease) is an alternative approach aiming at skipping the first phases of drug development (pre-clinical phase and safety tests in humans). It was estimated that repositioning a drug costs on average $300 million and takes around 6.5 years (Nosengo, 2016). Interestingly, the first drug reported to have antidepressant effects was iproniazid, an antitubercular compound which showed as "side effects" euphoria, psychostimulation, increased appetite, and improved sleep (Hillhouse and Porter, 2015). Serendipity apart, repurposing can be guided by different types of experimental data, for example *in vitro* cellular assays, animal models, or biomarkers of disease in affected populations. For example, genes associated with a disease may be used to identify potential pharmacological targets, a strategy that seems very promising as selecting genetically supported targets could double the success rate in clinical development (Nelson et al., 2015).

Previous studies used genetic markers of MDD to guide the identification of drugs that may be repurposed for the treatment of this disorder. The overlap between genes associated with MDD and known drug targets suggested some possible mechanisms of action, including dopamine receptor modulation, estrogen receptor modulation, calcium channels modulation and antagonism, acetylcholine receptor M3 antagonism, and histone deacetylase inhibition (So et al., 2019) (Zhao and So, 2019) (Gaspar et al., 2019) (So et al., 2017). However, these studies did not specifically focus on genetic markers of TRD, which may only partially overlap with those of MDD.

The present study aimed to identify new possible pharmacological options for TRD by comparing genes previously associated with this phenotype and known drug targets. We specifically used TRD as phenotype in order to increase the chances to identify drugs that may be effective in this group of patients with MDD who poorly respond to drugs acting through the modulation of monoaminergic neurotransmission.

2. Methods

2.1. Gene-drug targets databases

Genes coding for targets of drugs in any phase of development (from pre-clinical to launched), nutraceuticals, proteins and peptides were obtained from three publicly available databases: Drug-Gene Interaction (DGI) database, Drug Repurposing Hub (DRH) and DrugBank. The DGI database includes a combination of expert curation and text-mining from a number of sources (e.g. therapeutic target database, PharmGKB, ClinicalTrials.gov) (Cotto et al., 2018). This database also included drug classes (e.g. non-steroidal anti-inflammatory drugs). DRH is a manually curated source, compound samples were registered in the Broad compound management system and annotated for a number of characteristics (Corsello et al., 2017). DrugBank is expert curated and includes not only drugs but also proteins, peptides, and nutraceuticals (Wishart et al., 2018).

Drugs and other compounds from these datasets were merged based on their CHEMBL ID or chemical name when CHEMBL ID was not available.

2.2. Genes associated with treatment-resistant depression

We selected the gene sets previously demonstrated to predict the risk of TRD in a whole exome sequence and genome-wide association study on 1209 patients with MDD (Fabbri et al., 2020). These included a total of 1715 genes, which are mainly involved in the regulation of cell survival and proliferation, neurodegeneration and immune response. These genes consisted in four groups: 1) genes predicting TRD in patients treated with mixed antidepressants (n=17); 2) genes predicting TRD in patients treated with serotonergic antidepressants (n=83); 3) genes in pathways predicting TRD in patients treated with mixed antidepressants (n=216); 4) genes in pathways predicting TRD in patients treated with treated with serotonergic antidepressants (n=1398). These four groups were analysed separately since they were obtained in groups of patients treated with drugs having distinct pharmacologic domains or they reflected different prediction approaches (using genes or pathways as predictors of TRD).

2.3. Statistical analysis

For each molecule available in the described gene-drug target databases, we performed a hypergeometric test to evaluate if it was enriched in genes associated with TRD in any of the four groups described in paragraph 2.2 and kept the most significant finding when we observed enrichment in more than one of the four gene groups. The hypergeometric test measures the statistical significance of having drawn a sample consisting of a specific number of k successes (out of n total draws) from a population of size N containing K successes. In this case, k represents the number of genes targeted by a molecule/drug which are also associated with TRD, n is the total number of genes associated with TRD, N is the total number of genes tested and K is the total number of genes targeted by the molecule/drug. The test was performed using R cran as follows: phyper(k - 1, n, N - n, K, lower.tail=FALSE) and the Benjamini & Hochberg false-discovery rate (FDR) correction was applied to account for multiple-testing. We finally compared the significant results with the molecules showing enrichment in genes associated with MDD (considering loci, gene and pathway analyses) in a large genome-wide association study (Wray et al., 2018). The workflow is described in Figure 1.

3. Results

We found 3560 molecules available in at least two databases, while 9126 available in only one; each molecule had on average 3.28 gene targets (SD=6.77). The number of available molecules in each dataset is reported in Supplementary Table 1.

A total of 612 molecules and 10 classes enriched for TRD-associated genes were identified (FDR p<0.05) and their annotations are reported in Supplementary Table 2, while a summary description is in Table 1. Molecules showing enrichment for TRD-associated genes had a higher probability of enrichment for MDD-associated genes compared to those having no TRD-genes enrichment (p<2.2e-16), in line with what expected. Drugs with known therapeutic effect in TRD showed enrichment in TRD-associated genes, such as lithium (FDR p=9.25e-05), tricyclic antidepressants (FDR p=2.68e-03) and ketamine (FDR p=1.22e-02), demonstrating the validity of the approach. TRD-associated genes generally showed higher probability to be druggable than what expected by chance (genes in pathways predicting TRD in patients treated with mixed antidepressants and serotonergic antidepressants: p=2.49e-12 and p=2.10e-105, respectively; genes predicting TRD in patients treated with mixed antidepressants and serotonergic antidepressants: p=0.038 and p=0.61, respectively). In order to exclude that this result could be caused by a general higher druggability of genes in pathways compared to genes not belonging to known pathways, we extracted random sets of genes having the same size of the tested ones from known pathways 10,000 times. The mean number of druggable genes found in the random pathways was significantly lower compared to the tested pathways (61 and 328, p=0.0078 and p=7.27e-17 for those associated with resistance to mixed antidepressants and serotonergic antidepressants, respectively).

The most common mechanisms of action of molecules which targets were enriched in TRD-associated genes were modulation of cell proliferation/survival (31%), monoamine neurotransmission (14%) and modulation of inflammation and extracellular matrix (13%). Not surprisingly, the second group included the highest percentage of drugs approved/studied for the treatment of psychiatric disorders (26%). Other groups that included drugs approved/studied for psychiatric disorders were modulators of glycogen synthase kinase 3 beta (GSK3), modulators of vasopressin, angiotensin and/or oxytocin, drugs acting on cholinergic neurotransmission and GABAergic/glutamatergic neurotransmission (Table 1), though in some cases there were molecules in an earlier phase of clinical research or still not registered (e.g. pre-clinical studies) for the treatment of psychiatric illnesses (see notes in Supplementary Table 2). An example of this case was represented by peroxisome proliferator-activated receptor (PPAR) agonists and naturally occurring compounds with antioxidant/anti-inflammatory activity (e.g. ellagic acid), as described in detail in the Discussion. The proportion of molecules in the post-marketing phase or phase 2-3 was variable, but it was usually at least 50% for the drug groups including at least ten molecules (Table 1), therefore providing a quite rich pool of potential candidates that already passed phase 1 of development.

4. Discussion

The present study aimed to identify possible candidate drugs for repositioning in TRD by testing known drug gene targets for enrichment in TRD-associated genes. The results suggested about 600 possible candidate compounds, including not only drugs but also peptides and nutraceuticals. Drugs with indication for the treatment of TRD were included, such as lithium, ketamine and several antidepressants, confirming the rationale of the approach. In terms of mechanisms of action, the largest group was represented by modulators of cell proliferation/survival, in line with the observation that neural survival and neurogenesis are implicated in the pathogenesis of depression (Miller and Hen, 2015). However, this group mostly included drugs studied or approved for the treatment of various types of cancer, working through the inhibition of cellular signalling cascades controlled by growth factor receptors, and this is clearly not a therapeutic option for TRD as it would produce negative rather than beneficial effects. This reflects the main limitation of the present approach: it does not distinguish the direction of the effect (therapeutic or noxious) of drugs which targets are enriched in TRD-associated genes. However, this could be inferred from the mechanisms of drug action, thus the present results can provide meaningful information after proper interpretation. Drugs with interesting mechanisms of action based on the literature and previous evidence of possible antidepressant effects are therefore discussed in the next sections to provide cues on potential new treatments for TRD (Table 2).

4.1. Renin-angiotensin system modulators

A total of 22 molecules had this as primary mechanism of action, for example telmisartan, captopril and nelivaptan. The renin-angiotensin system (RAS) does not play a role only in the modulation of the cardiovascular system, but it also has important regulatory functions in the brain. Angiotensin receptors (primarily AT1R) are indeed expressed in the brain where angiotensin II (Ang II) is implicated in multiple pathways related to regulation of the stress response. For example, the activation of AT1R contributes to the release of inflammatory cytokines (e.g. tumour necrosis factor α), to oxidative and nitrosative stress, and to the increase in the production of corticotrophin-releasing factor (Vian et al., 2017). AT2R is involved in neurodevelopment, extracellular matrix modulation, neuronal regeneration, apoptosis and cellular differentiation, and other components of the RAS system such as ACE2 and angiotensin-(1–7) were demonstrated to play a role in processes relevant to neuroprotection and neurotoxicity (Vian et al., 2017). In animal models, the blockage of Ang II has antidepressant-like and anti-anxiety effects and confirmed the anti-inflammatory and oxidative stress-reducing effects as part of the mechanisms of action of AT1R antagonists and ACE inhibitors (ACEIs) (Vian et al., 2017). Though there are not randomized controlled trials (RCTs) investigating the potential antidepressant effect of these drugs in humans, the results of observational or case control studies suggested that persons exposed to ACEIs have a lower risk of MDD compared to other antihypertensive drug classes (Rathmann et al., 1999) (Williams et al., 2016) (Boal et al., 2016). A recent meta-analysis of eleven studies reported that compared with placebo or other antihypertensive medications, AT1R blockers and ACEIs were associated with improved overall quality of life, increased wellbeing, improved mental health and anxiety domains of quality of life, though no significant difference was found for the depression domain (Brownstein et al., 2018).

4.2. Glycogen synthase kinase 3 beta (GSK3B) inhibitors

GSK3B is implicated in the pathogenesis of mood disorders, anxiety, response to reward and in antidepressant action through several mechanisms. One of the mechanisms of action of lithium and

atypical antipsychotics having indications in mood disorders is the inhibition of GSK3B (Li and Jope, 2010) and GSK3B inhibition is necessary for the rapid antidepressant effects of ketamine in mice (Beurel et al., 2011, p. 3). GSK3B regulates the activity of proteins with mood-regulating functions, such as the transcription factor cyclic AMP response element-binding protein (CREB), β-catenin, disrupted in schizophrenia 1 (DISC1), serotonin receptors, N-methyl-D-aspartate (NMDA) receptor, inflammatory cytokines; therefore it has an impact on neuroprotective mechanisms, neuroplasticity and stress response (Li and Jope, 2010). Mice with mutations blocking the inhibition of GSK3B and GSK3alpha showed increased susceptibility to both amphetamine-induced hyperactivity and stress-induced depressive-like behaviours, but not altered baseline behaviours, suggesting that insufficient inhibitory serine phosphorylation of GSK3 is a risk factor for developing mood-related behavioural disturbances (Li and Jope, 2010).

Among the compounds which targets were enriched in TRD-associated genes, the selective, potent, ATP-competitive GSK3 inhibitor CHIR99021 was shown to be well-tolerated and significantly ameliorated mood-related behaviours in mice (Pan et al., 2011). SB-415286 and TWS119 were demonstrated to have neuroprotective effects and induce neural differentiation of stem cells (Dill et al., 2008) (Ding et al., 2003). Both alsterpaullone and kenpaullone prevented neuron cell death in response to variety of insults including trophic deprivation, thapsigargin treatment, and mitochondrial stress (Eldar-Finkelman and Martinez, 2011). It has been suggested that GSK3 inhibition may potentiate the synaptogenic and antidepressant-like effects of ketamine and could make effective subthreshold doses of ketamine (Liu et al., 2013).

4.3. Proliferator-activated receptor agonists and nitric oxide inhibitors

Proliferator-activated receptor (PPAR) agonists are a class of medications for the treatment of insulin resistance in type 2 diabetes; interestingly, there is a link between insulin resistance and related pathophysiological changes with depressive symptoms. Insulin resistance is indeed associated with pro-inflammatory changes, mitochondria abnormalities, oxidative stress and modifications in the release and reuptake of monoamine neurotransmitters (Kemp et al., 2014). Animal studies demonstrated that PPAR agonists such as pioglitazone have antidepressant-like properties and suggested that the nitric oxide (NO) pathway is partially responsible for this effect (Eissa Ahmed et al., 2009) (Sadaghiani et al., 2011). NO is a gaseous neurotransmitter generated from L-arginine by the enzymes NO synthase (NOS), which are expressed in three isoforms in the brain, neuronal NOS (nNOS), endothelial NOS (eNOS) and inducible NOS (iNOS), with nNOS representing the major source for NO synthesis, anchored in close proximity to N-methyl-d-aspartate (NMDA) receptors. NO plays a role in synaptic homeostasis and exerts various neuromodulatory effects as well as promotes neuronal plasticity. Imbalances in NOS activity have been demonstrated in depression and response to stress; aminoguanidine and other NOS inhibitors were shown to have antidepressant-like effects in animal models of depression (Joca et al., 2019).

PPAR agonists (pioglitazone or rosiglitazone) were shown to have antidepressant effects in four open-label studies and in three out of four RCTs in patients with major depression (Colle et al., 2017). In patients with concomitant metabolic syndrome or related disorders such as abdominal obesity these drugs were reported not only to improve depressive symptoms but also markers of cardiometabolic risk, including insulin resistance and inflammation biomarkers (Kemp et al., 2012) (Kemp et al., 2014). According to these studies, patients with bipolar or unipolar depression who did not respond to previous pharmacological treatments (treatment-resistant depression) may benefit from pioglitazone or rosiglitazone. Both these drugs are selective for the gamma subtype of PPAR

(PPARγ), but also PPARα modulate antioxidant responses, neurotransmission, neuroinflammation and neurogenesis; as a matter of fact, fenofibrate, a selective agonist of PPARα, had significant antidepressant-like effects in mice via enhancing the hippocampal BDNF system, while PPARα antagonism blocked the effects of both fenofibrate and fluoxetine (Song et al., 2018). Interestingly, PPAR agonists were identified also in a previous drug repurposing study for MDD (So et al., 2017). A related drug class that may have beneficial effects for the treatment of depressive symptoms in comorbidity with metabolic abnormalities is represented by HMG-CoA reductase inhibitors (statins). Preliminary RCTs have indeed indicated that statins may have adjunctive antidepressant effects when used as add-on treatment to selective serotonin reuptake inhibitors (SSRIs) (Köhler-Forsberg et al., 2017).

4.4. Modulators of inflammation and immune system
Several members of this group were previously studied for the treatment of depression as augmentation to antidepressants, such as acetylsalicylic acid, celecoxib and other non-steroidal anti-inflammatory drugs that were enriched in TRD-associated genes (Andrade, 2014) (Kopschina Feltes et al., 2017). These drugs act through the inhibition of cyclooxygenases (COXs) that are key enzymes in the production of prostaglandins, implicated in inflammatory response, pain and autonomic functions (Kopschina Feltes et al., 2017).

An alternative mechanism that may be considered for the modulation of inflammation in depression is represented by the inhibition of the p38 mitogen-activated protein (p38-MAPK) signaling pathway. This pathway is activated in response to various stress stimuli, including post-traumatic stress (Lizama et al., 2009) (Peng et al., 2013). Stressed mice subjected to intrahippocampal or intraventricular injections of the p38 inhibitor SB203580, which targets are enriched in TRD-associated genes, exhibited fewer depression- and anxiety-like behaviors (Zhao et al., 2018) (Han et al., 2019). The p38-MAPK pathway modulates a variety of cellular process, but its role in the regulation of neuroinflammation in regions relevant to emotion regulation was proposed as a key contributor to its effects on depressive behaviors (Zhao et al., 2018). Drugs acting through the inhibition of p38-MAPK could also have pro-cognitive effects as shown for neflamapimod (Ardura-Fabregat et al., 2017).

Inhibitors of pro-inflammatory cytokines are a further group of drugs with potential application for the treatment of TRD. An example is anakinra (an interleukin 1 receptor antagonist) which is approved for the treatment of rheumatoid arthritis and it was associated with an improvement in mood in patients with this disorder (Koo and Duman, 2009).

Several of the identified drugs are modulators of matrix metalloproteinases (MMPs), which may play a role in antidepressant effects. MMPs target various substrates in the brain, and they modulate adaptive brain plasticity, inflammation and cytotoxicity through the modelling of the perineuronal net. Various antidepressant medications increase the expression of MMPs, which in turn may increase pyramidal cell dendritic arborization and spine formation (Alaiyed and Conant, 2019). However, the large range of processes regulated by MMPs, depending from MMPs subtypes and localization, makes them a non-easy pharmacological target for depression. None of the identified molecules were studied for the treatment of depression, apart from doxycycline, which at subantimicrobial doses is an inhibitor of MMPs and showed antidepressant-like effects in lipopolysaccharide-induced depressive behavior in mice (Mello et al., 2013). Doxycycline was among the identified drugs in a previous drug repurposing study for MDD (So et al., 2017).

Recently, the inhibition of rapamycin complex 1 (mTORC1) by pre-treatment with rapamycin in patients receiving ketamine was unexpectedly shown to prolong the antidepressant effects of ketamine rather than inhibiting them as suggested by animal models. One of the possible mechanisms explaining this finding may consist in the anti-inflammatory effect of rapamycin via mTORC1 inhibition that may protect ketamine-induced newly made synapses from elimination (Abdallah et al., 2020).

4.5. Modulators of GABAergic and glutamatergic neurotransmission

Within this group, ketamine has already strong evidence of efficacy in TRD (Kraus et al., 2019). Other glutamate receptor antagonists which targets were enriched in TRD-associated genes were dextromethorphan and spermidine. Spermidine (as well as spermine and agmatine) is a short, positively charged aliphatic amine that have fundamental roles in homeostatic mechanisms, including the modulation of NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamatergic receptors and therefore neuronal excitability. Polyamine levels have been demonstrated to increase during stress, a phenomenon called the polyamine stress response, and they have been implicated in MDD and suicide (Limon et al., 2016). Spermidine is also involved in the regulation of aging and external supply of polyamines may protect against age-related memory loss, representing a possible therapeutic intervention that is currently under investigation (Wirth et al., 2019). Dextromethorphan is a medication approved as cough suppressant, however its effect on NMDA, sigma-1 and mu opioid receptors as well as the serotonin and noradrenaline transporters made it interesting as potential rapid-acting antidepressant (Lauterbach, 2011). A case report and an open-label trial of dextromethorphan in TRD showed good tolerability and preliminary evidence of efficacy (Lauterbach, 2016) (Murrough et al., 2017). The limited bioavailability of dextromethorphan and the risk of subtherapeutic doses led to the design of AVP-786, an oral formulation that combines dextromethorphan hydrobromide and quinidine sulfate to increase the bioavailability of the compound by decreasing the metabolism through CYP2D6. A phase two RCT aiming to evaluate the efficacy of AVP-786 in TRD has been completed in 2016, but the results are still not published (ClinicalTrials.gov Identifier: NCT02153502).

Modulators of L-glutamine, the precursor of glutamate and GABA, are also potentially interesting molecules for TRD. Perturbations in glutamine levels may alter neuronal-astrocytic interactions (Struzyńska and Sulkowski, 2004) and glutamine deficiency in the pre-frontal cortex was reported to increase depressive-like behaviors in mice (Lee et al., 2013). Inhibition of glutamate synthetase by methionine sulfoximine decreased glutamate and glutamine levels and increased depressive behaviors, a condition that was reversed by exogenous glutamine (Son et al., 2018). Changes in the glutamine/glutamate ratio were associated with the efficacy of ketamine and other compounds such as cytidine in improving depressive symptoms (Yoon et al., 2009) (Li et al., 2017).

Among modulators of GABAergic neurotransmission, tiagabine and vigabatrin were enriched in TRD-associated genes. Vigabatrin was shown to have antiepileptogenic and antidepressant properties in an animal model of depression and comorbid epilepsy (Russo et al., 2011), but it has no evidence of antidepressant effects in humans. Tiagabine has known effects as mood stabilizer, antidepressant and anxiolytic-like effects that may partly dependent from a modulation of the hypothalamic pituitary adrenal (HPA) axis in animal models, and it has been proven effective in patients with generalized anxiety disorder (Sałat et al., 2015) (Thoeringer et al., 2010) (Strawn et al., 2018).

4.6. Natural compounds

The glutathione precursor N-acetyl-l-cysteine (NAC) was included in this group, a compound studied as add on to antidepressants in TRD for its known positive effects on neuro-inflammation, glutamate neuronal activity and neurogenesis (Yang et al., 2018).

Several polyphenolic compounds with antioxidant properties (flavonoids) were enriched in TRD-associated genes; these included ellagic acid, epigallocatechin gallate, quercetin, resveratrol, clove oil and sho-saiko-to (which main component is baicalein in wogon (Makino et al., 2006)). Ellagic acid occurs largely in plants such as raspberries, the stem and bark of eucalyptus species and nuts, while epigallocatechin gallate and quercetin are found in green/black tea, the latter and resveratrol in red wine (Girish et al., 2012) (Rothenberg and Zhang, 2019) (Hritcu et al., 2017) (Zhu et al., 2019). Bioflavonoids have been reported to have antioxidant, anti-inflammatory, cardio-protective and anticancer properties. Antidepressant-like effects were observed in mice and they were linked to the modulation of the monoaminergic system (particularly, increase of serotonin and norepinephrine availability in the synaptic cleft), increased BDNF level in mice hippocampus, NOS inhibition, restoration of HPA dysfunctions and suppression of the microglial neuroinflammatory response (Girish et al., 2012) (Bedel et al., 2018) (Dhingra and Chhillar, 2012) (Rothenberg and Zhang, 2019) (Hritcu et al., 2017) (Zhu et al., 2019). Both resveratrol and ellagic acid were identified also in a previous drug repurposing study for MDD (So et al., 2019).

Clove oil (*Syzygium aromaticum*) is a traditional spice that has been used for food preservation and it has several active constituents, including phenolic compounds, sesquiterpenes, and monoterpenes. It has documented pro-cognitive, analgesic, cardio-protective, anti-inflammatory and antidepressant-like effects; the latter were attributed to the inhibition of monoamine oxidase A by the active component eugenol (El-Saber Batiha et al., 2020).

Sho-saiko-to (or xiǎocháihútāng, XCHT) is a traditional Chinese medicine which was first recorded in 150–219 AD to cure "Shaoyang syndrome", which included depressive symptoms such as upset and anepithymia. This compound was demonstrated to have antidepressant-like effects in animal models of depression by enhancing the serotoninergic system in the prefrontal cortex and hippocampus (Su et al., 2014).

Finally, zinc and selenium targets were also enriched in TRD-associated genes. These are essential trace elements involved in antioxidant and other cellular processes relevant to brain metabolism. Zinc deficiency has been associated with depression in a meta-analysis of 17 observational studies and RCTs have demonstrated decreases in depressive symptoms when supplementing antidepressants with zinc compared to antidepressants alone (Wang et al., 2018). Possible mechanisms involved in this positive effect include the modulation of NMDA receptors, HPA axis, zinc-sensing GPR39 receptors, anti-inflammatory and antioxidant properties and NOS inhibition (Wang et al., 2018). Selenium deficiency was associated with decreased BDNF concentrations and supplementation of selenium showed antidepressant-like effects in animal models of depression, though studies in humans provided inconsistent results (Wang et al., 2018).

Therefore, the evaluation of possible deficits of these elements in patients with depression is particularly relevant. Zinc is primarily consumed through red meats and seafood, diets that limit the consumption of these foods (e.g., vegetarianism, veganism) may alter serum zinc levels. Selenium deficiency often results from suboptimal presence in regional soil, making selenium deficiency often an endemic issue (Wang et al., 2018).

4.7. Other mechanisms

Modulation of estrogen and androgen receptors has been studied as a possible strategy to treat depressive symptoms and has emerged in previous drug repurposing studies (Gaspar et al., 2019), though it should be considered only in selected groups of patients (peri- or post-menopausal women (Morgan et al., 2005), hypogonadal men (Amiaz and Seidman, 2008)). Among the studied compounds, the neurosteroid dehydroepiandrosterone (DHEA) has emotion regulatory effects and plasma levels were associated with remission in MDD (Hough et al., 2017); DHEA was reported also by a previous drug repurposing study for MDD (So et al., 2019).

The therapeutic potential of cannabidiol in MDD emerged from this study as well as in a previous repurposing study (So et al., 2019). Cannabidiol, a non-psychotomimetic component of Cannabis sativa, shows both rapid and sustained antidepressant-like effects in animal models of depression, effects which were associated with an increase in BDNF levels in both prefrontal cortex and hippocampus (Sales et al., 2019) (Silote et al., 2019). A possible underlying mechanism is the modulation of serotonergic and glutamatergic cortical signaling through a 5-HT1A receptor-dependent activity (Linge et al., 2016).

The modulation of dopaminergic receptors is another pharmacological mechanism which has been long studied for the treatment of MDD and suggested by previous drug repositioning papers (Gaspar et al., 2019)(So et al., 2017). In this group, pramipexole is an interesting option. It is s a non-ergot dopamine agonist with high affinity for the D2, D3 and D4 dopamine receptors, approved for the treatment of Parkinson's disease and restless legs syndrome. Evidence of antidepressant efficacy compared to placebo was reported in a meta-analysis of five RCTs (Tundo et al., 2019) and one RCT showed superior efficacy of pramipexole augmentation to antidepressants vs. augmentation with placebo in TRD (Cusin et al., 2013).

Less investigated mechanisms of action that may be promising for the treatment of TRD include rho-kinase (ROCK) inhibitors, poly(ADP-ribose) polymerase (PARP) inhibitors and TGF beta agonists. ROCK inhibitors (e.g. fasudil) have rapid antidepressant-like effects in mice, comparable to ketamine, which is presumably linked to the promotion of activity-dependent dendritic spine pruning or spine head enlargement; ROCK indeed inhibits cofilin-mediated actin cycling, the process of change in size and shape of dendrites controlled by actin filaments (Shapiro et al., 2019). Compared to this mechanism which appears particularly innovative, the other mentioned ones involve alternative pathways to induce anti-inflammatory and/or neuroprotective/antioxidant effects which showed promising results in animal models of depression (Ordway et al., 2017) (Zhang et al., 2020).

4.8. Conclusions

The identification of effective and well-tolerated drugs with antidepressant effects in TRD is a challenging but vital task to reduce the burden of MDD to individuals and society. This study explored potential mechanisms alternative to the inhibition of monoamines reuptake using the results of a pharmacogenomic study and comparisons with the previous literature. Though the available evidence of antidepressant efficacy of the proposed compounds is variable, we provided useful information for future studies that may lead to innovative treatments for TRD.

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