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INVITED REVIEW

Antihypertensive drugs and brain function: mechanisms underlying therapeutically beneficial and harmful neuropsychiatric effects

Carla Carnovale [1†], Cristiana Perrotta [1†], Sara Baldelli [2], Dario Cattaneo [2], Cristina Montrasio [2], Silvia S. Barbieri [3], Giulio Pompilio [4,5], Chiara Vantaggiato [6], Emilio Clementi [1,6*‡], and Marco Pozzi [6‡]

[1]Unit of Clinical Pharmacology, Department of Biomedical and Clinical Sciences (DIBIC), ASST Fatebenefratelli-Sacco University Hospital, Università degli Studi di Milano, Via GB Grassi 74, 20157 Milano, Italy; [2]Unit of Clinical Pharmacology, ASST Fatebenefratelli-Sacco University Hospital, 20157 Milano, Italy; [3]Unit of Brain-Heart Axis: Cellular and Molecular Mechanisms – Centro Cardiologico Monzino IRCCS, 20138 Milano, Italy; [4]Unit of Vascular Biology and Regenerative Medicine – Centro Cardiologico Monzino IRCCS, 20138 Milan, Italy; [5]Department of Biomedical, Surgical and Dental Sciences, Università degli Studi di Milano, 20122 Milan, Italy; and [6]Scientific Institute IRCCS Eugenio Medea, 23842 Bosisio Parini (LC), Italy

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Abstract

A bidirectional relationship exists between hypertension and psychiatric disorders, including unipolar and bipolar depression, anxiety, post-traumatic stress disorder (PTSD), psychosis, schizophrenia, mania, and dementia/cognitive decline. Repurposing of antihypertensive drugs to treat mental disorders is thus being explored. A systematic knowledge of the mechanisms of action and clinical consequences of the use of antihypertensive agents on neuropsychiatric functions has not been achieved yet. In this article, we review the putative role of antihypertensive agents in psychiatric disorders, discuss the targets and mechanisms of action, and examine how and to what extent specific drug classes/molecules may trigger, worsen, or mitigate psychiatric symptoms. In addition, we review pharmacokinetics (brain penetration of drugs) and pharmacogenetics data that add important information to assess risks and benefits of antihypertensive drugs in neuropsychiatric settings.

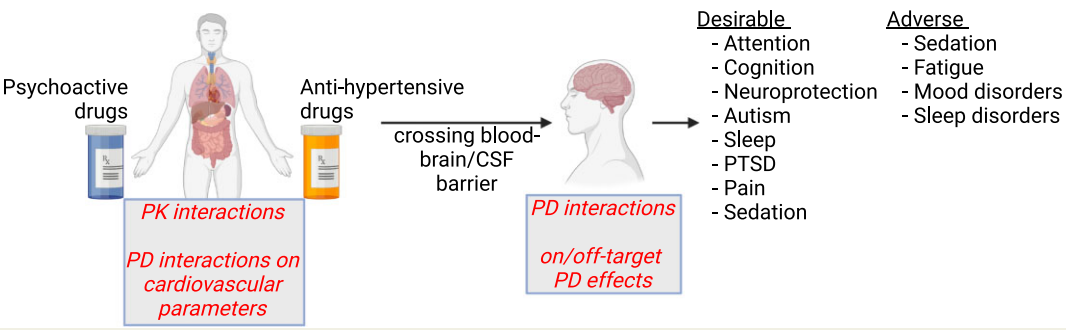
The scientific literature shows robust evidence of a positive effect of α1 blockers on PTSD symptoms, nightmares and sleep quality, α2 agonists on core symptoms, executive function, and quality of life in Attention-Deficit/Hyperactivity Disorder, PTSD, Tourette's syndrome, and β blockers on anxiety, aggression, working memory, and social communication. Renin-angiotensin system modulators exert protective effects on cognition, depression, and anxiety, and the loop diuretic bumetanide reduced the core symptoms of autism in a subset of patients. There is no evidence of clear benefits of calcium channel blockers in mood disorders in the scientific literature. These findings are mainly from preclinical studies; clinical data are still insufficient or of anecdotal nature and seldom systematic. The information herewith provided can support a better therapeutic approach to hypertension, tailored to patients with, or with high susceptibility to, psychiatric illness. It may prompt clinical studies exploring the potential benefit of antihypertensive drugs in selected patients with neuropsychiatric comorbidities that include outcomes of neuropsychiatric interest and specifically assess undesirable effects or interactions.

* Corresponding author. Tel +39 02 50319643; fax: +39 02 50319682, E-mail: emilio.clementi@unimi.it

† C.C. and C.P. contributed equally to the manuscript.

‡ E.C. and M.P. are joint last authors.

Graphical Abstract



Keywords Antihypertensive drugs • Neuropsychiatric disorders • Personalized medicine

1. Introduction

The mind–heart–body relationship, specifically the connection between mental disorders and cardiovascular diseases, has received considerable attention in the last decades. Consistent evidence indicates that patients suffering of both cardiovascular diseases and psychiatric disorders (e.g. depression, anxiety, post-traumatic stress, schizophrenia, dementia, and cognitive decline) have a lower quality of life and are at higher risk of mortality.[1–5] Hypertension not only is a major risk factor for cardiovascular diseases but also is related to mental health problems such as anxiety and depression. Hypertensive patients are more likely to have a recorded diagnosis of mental disorders, and hypertension increases the severity of psychological distress. Conversely, prospective studies showed that psychiatric disorders are independent risk factors for hypertension. Mental disorders can cause continuous activation of the sympathetic nervous system and dysfunction of the hypothalamus-pituitary-adrenaline axis, thus increasing vascular tone and blood pressure and leading to pathological hypertension disorders.[6] In conclusion, a clinically significant bidirectional relationship between these two disorders exists,[7–9] leading to a vicious cycle that contributes to worsen their outcome. Proper psychiatric and hypertensive management may be crucial to prevent complications in these patients.

Based on this knowledge, in recent years the possibility of repurposing antihypertensive drugs to treat mental disorders has been explored: notable examples include diuretics (bumetanide) for autism and

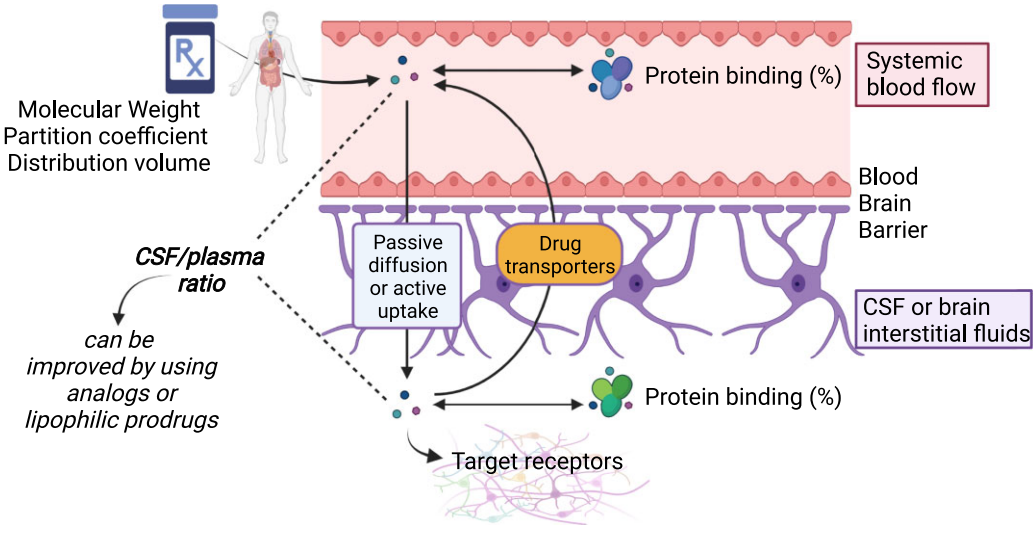


Figure 1 Brain penetration of anti-hypertensive and other drugs. Brain penetration of anti-hypertensive drugs is regulated by some intrinsic chemical properties, including molecular weight, partition coefficient, and distribution volume: these regulate the overall permeability of drugs through biological membranes. Once drugs are absorbed and distributed in the blood flow, they are bound by plasma proteins. The unbound fraction can cross the BBB either passively or actively, and it is often sent back to the blood flow by drug transporters. Once in the cerebrospinal fluid (CSF) or brain interstitial fluids, again drugs can be bound. Unbound fractions in the brain can actually bind their receptors and produce effects. Created with BioRender.com.

Table 1 Physico-chemical and pharmacokinetic features of the main anti-hypertensives from different classes

	Molecular weight (Da)	Log p	Vd (L/kg)	Protein binding (%)	CSF/plasma ratio, %	Drug transporters
ACEIs						
Captopril	217	0.3	0.7	30%	Not available	Inhibitor of P-gp
Enalapril	376	2.5	2.0	50%	Not available	Substrate of OATP1 and MRP2
Lisinopril	405	−1.3	1.8	<1%	Not available	
Trandolapril	431	1.9	0.3	80%	Not available	
Ramipril	416	2.9	1.2	70%	2%	
CCB						
Amlodipine	409	3	21.4	98%	Not available	Substrate and inhibitor of P-g
Verapamil	455	1.8	3.8	88%	7%	Substrate and strong inhibitor of P-gp
Nifedipine	346	2.2	13	95%	Not available	Inhibitor of P-gp
Felodipine	383	3.8	10	99%	Not available	Substrate of P-gp
Diltiazem	414	3	5.3	75%	10%	Substrate and inhibitor of P-gp
Beta-blockers						
Bisoprolol	325	2.2	3.5	30%	55%	Inhibitor of P-gp
Metoprolol	267	2.1	4.0	10%	43%	
Atenolol	266	0.2	0.7	3%	10%	
Propanolol	259	3.5	4.0	90%	5%	Substrate and inducer of P-gp
Carvedilol	406	3.8	1.6	95%	Not available	Strong inhibitor of P-gp
Diuretics						
Bumetanide	364	2.1	0.44	96%	2%	Substrate of OATP1 and MRP4
Furosemide	331	1.8	0.14	99%	Not available	Substrate of MRP4 and BCRP
Torasemide	348	3.4	0.2	99%	Not available	Substrate of SLCO1B1
Chlorthalidone	339	0.9	3.9	75%	Not available	
Hydrochlorothiazide	298	−0.1	2.0	58%	4%	Substrate of MRP4

CCB, calcium channel blockers; P-gp, P-glycoprotein.

epilepsy,[10] and AT1R blockers (ARBs) and calcium channel blockers (CCBs) for Alzheimer's dementia.[11] From a clinical perspective, it is important to clarify how and to what extent antihypertensive drugs would exert neuropsychiatric effects, both desirable and adverse, also in view of managing combined therapies. In this review, we provide an overview of essential aspects of the pharmacokinetics and pharmacogenetics of the different pharmacological classes of antihypertensive drugs. For each class, we describe the receptors and molecular mechanisms through which antihypertensive drugs generate neuropsychiatric effects in preclinical models, highlighting those that, in our opinion, are desirable and potentially exploitable in therapy. We then discuss drug-drug interactions with commonly prescribed psychiatric drugs, focussing only on psychiatric aspects, while metabolic issues are reviewed elsewhere.[12,13] Lastly, we report the results of a systematic review that we performed on data from clinical studies included over the last 20 years in the most popular bibliographic database in health and medical sciences, PUBMED/Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica database (EMBASE), and Psycinfo that provides systematic coverage of literature in the field of psychology. In this context, we describe the psychiatric effects of antihypertensive drugs and, where relevant, the pharmacological aspects that may influence such effects.

This article aims to stimulate future clinical research studies and promote a conscious tailored therapeutic approach to hypertension in patients with, or with high susceptibility to, psychiatric illness.

2. Central nervous system penetration of anti-hypertensive drugs

The ability of anti-hypertensive drugs to exert their potential neurological effects is linked to the capability of these compounds to cross the blood–brain barrier (BBB) and/or the blood cerebrospinal fluid barrier (BCSFB) and reach their therapeutic targets in the central nervous system (CNS) in sufficient concentrations.[14]

Drugs can pass the BBB and/or the BCSFB either by passive diffusion or by active uptake through specific trans-membrane protein transporters (carrier-mediated endocytosis) (*Figure 1*). Most small molecule drugs with high lipophilicity (molecular weight <400–600 Dalton; logarithm of the octanol/water partition coefficient, i.e. logP >1) are able to enter the brain by trans-cellular passive diffusion through the lipid membranes. However, the extent of brain penetration for these drugs depends also on the protein binding in blood and brain. Only the unionized, unbound drug concentration at the site of action leads to pharmacological activity; therefore, brain entry by passive diffusion may be significantly restricted for molecules with a high protein binding (>80%).

Furthermore, efflux transporters such as P-glycoprotein (P-gp), organic anionic transporters (OATPs), and breast cancer resistance protein (BCRP) protect the brain from penetration of harmful substances.

Table 2 Binding profile of antihypertensive drugs at selected receptors of neuropsychiatric interest

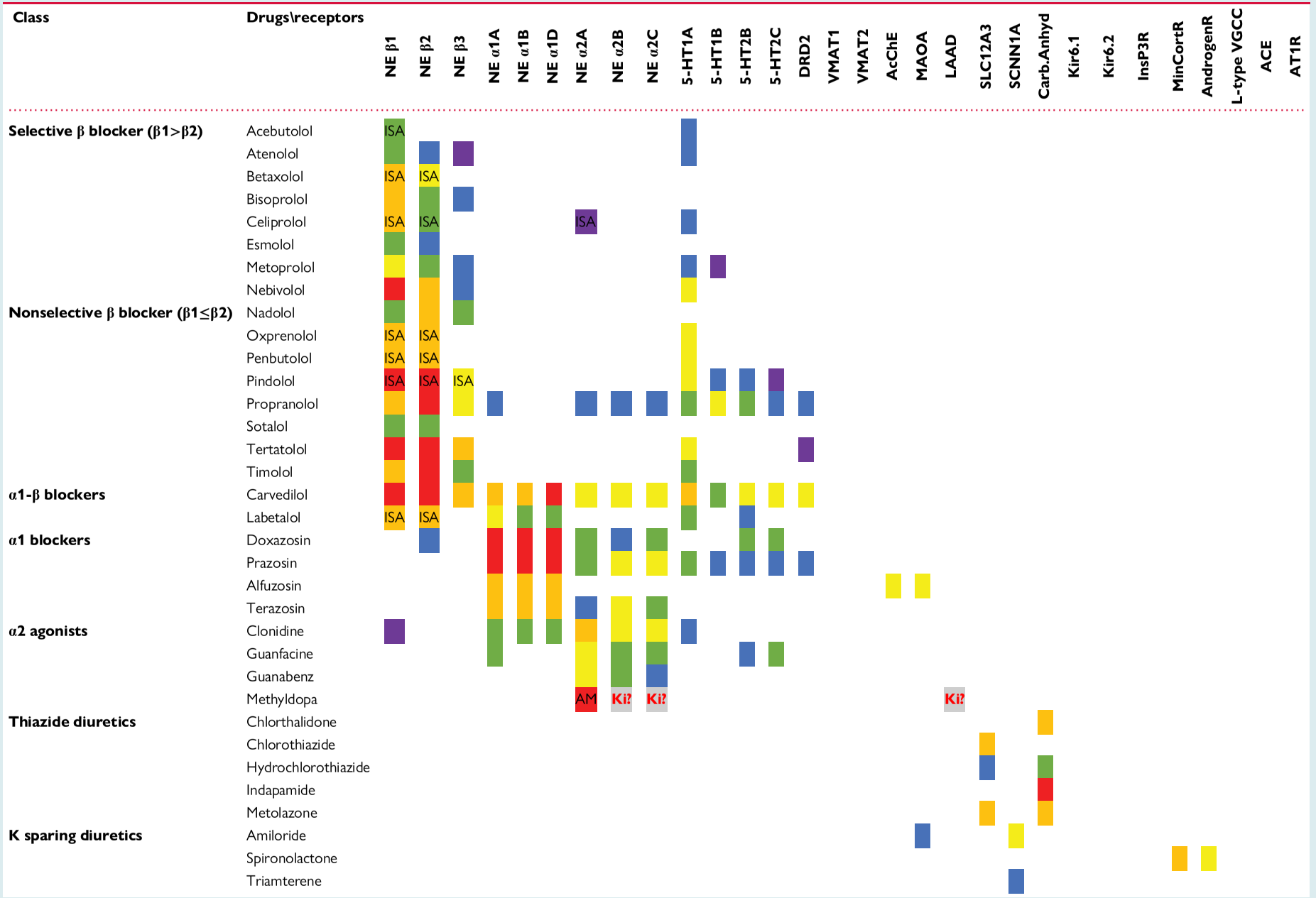


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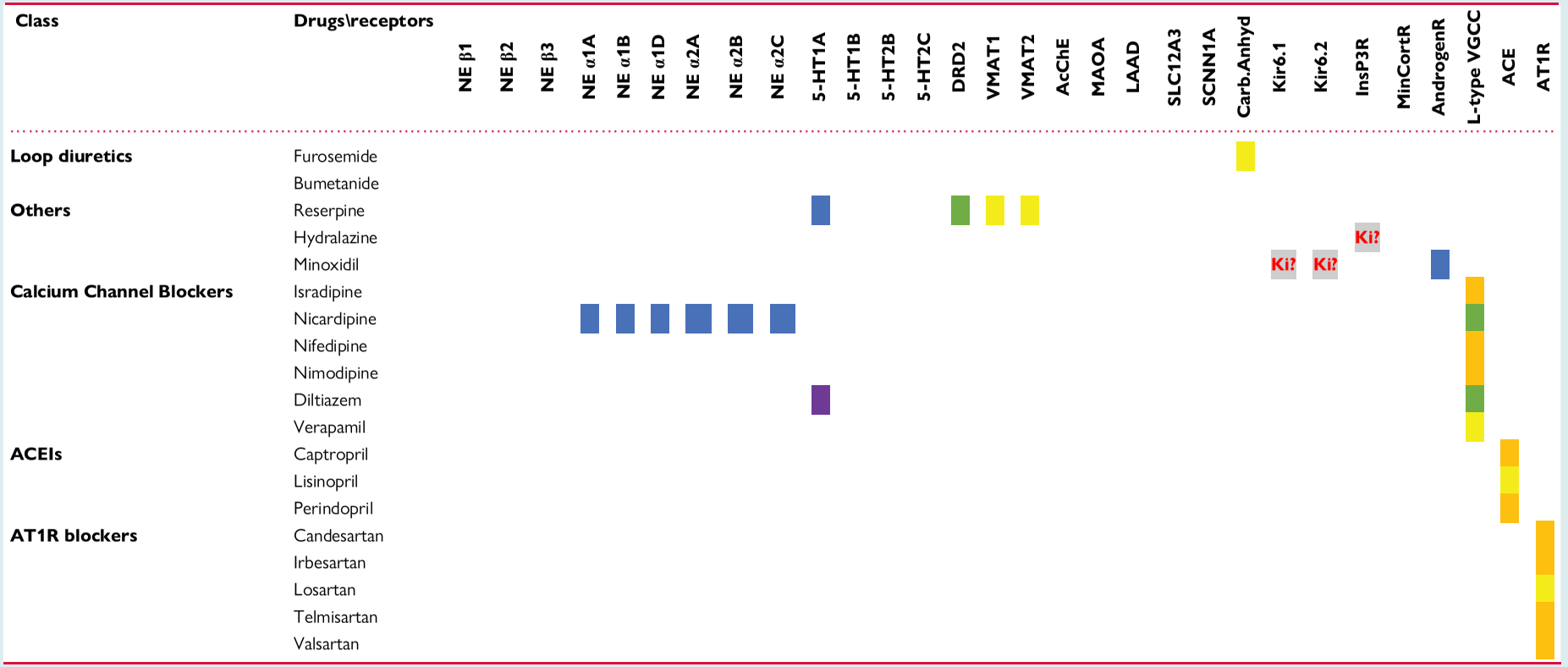
Table 2 *Continued*



Colours reported in each cell indicate the pKi for the specific binding between drugs (left) and receptors (top): red = pKi above 9; orange = pKi 8-9; yellow = pKi 7-8; green = pKi 6-7; blue = pKi 5-6; violet = pKi 4-5; gray = binding confirmed, but pKi not known. Only receptors for which at least one drug shows at least pKi >6 are shown.

AM, active metabolite; ISA, intrinsic sympathomimetic activity. Sources for parameters are the PDSP Database [Science Netwatch, 28 January 2000; 287 (5453)] and the Binding DB [Gilson, M.K., Liu, T., Baitaluk, M., Nicola, G., Hwang, L., and Chong, J. BindingDB in 2015: A public database for medicinal chemistry, computational chemistry and systems pharmacology Nucleic Acids Research 44:D1045-D1063 (2016)].

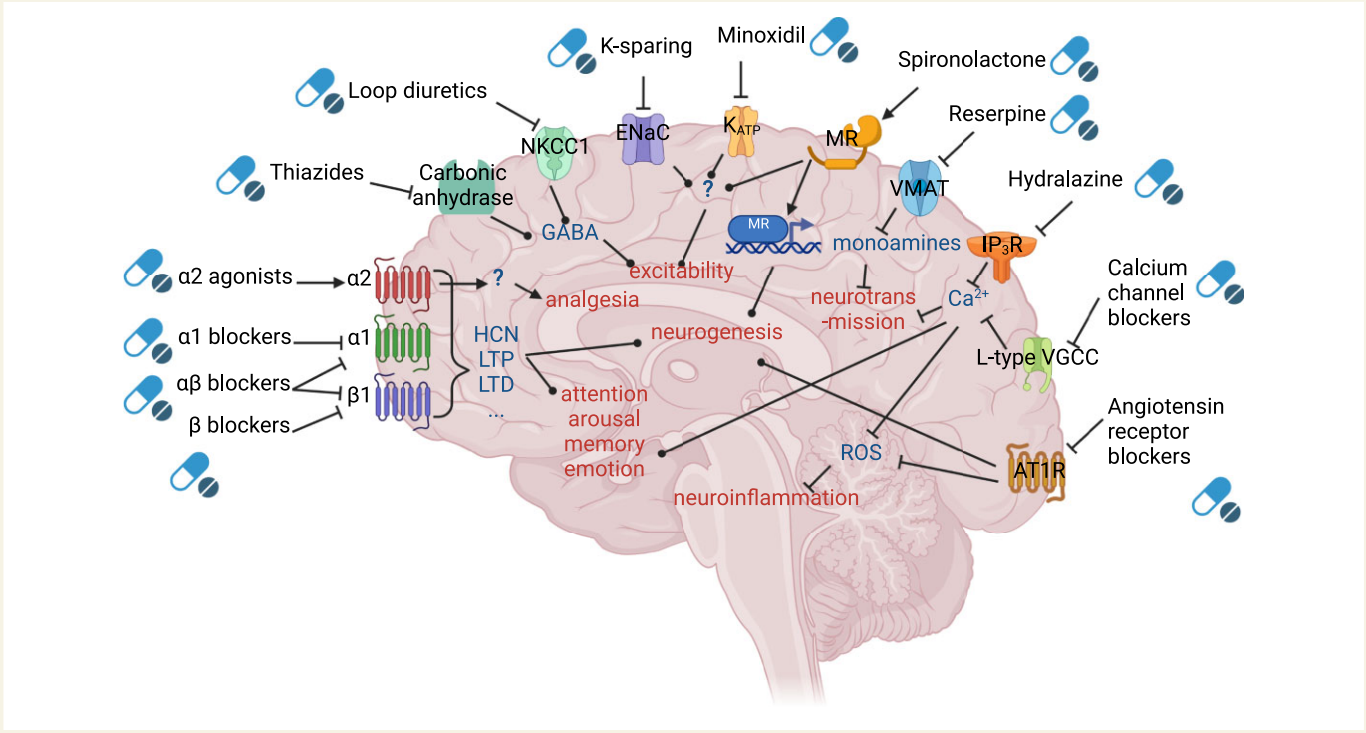


Figure 2 Main mechanisms of action of anti-hypertensive drugs in the brain. For each drug class, we reported on the brain surface the main molecular target in the brain; downstream, we reported the intermediate mechanisms of action; terminally, we reported the higher-level final mechanisms of action. The aspects and localizations of receptors and mechanisms are purely graphical and do not indicate molecular structures or anatomical localizations. Sharp-headed arrows indicate stimulation; flat-headed arrows indicate inhibition; circular-headed arrows indicate modulation. Created with BioRender.com.

Therefore, if a drug is substrate of these efflux transporters, it is less likely to penetrate into the brain (*Table 1*).

Table 1 provides the main physico-chemical and pharmacokinetic features of some antihypertensive drugs, which can be used to predict their ability to cross the brain barriers. This table is not intended to be exhaustive of all the antihypertensive drugs on the market; it aims to show that the capacity to penetrate the CNS can vary for molecules belonging to the same therapeutic category based on their chemical, physical, and pharmacokinetic characteristics. All antihypertensive drugs are small molecules and, therefore, potential candidates for passive diffusion. However, even within the same drug class, important differences exist in the lipophilicity of the different compounds. For instance, among the ACE inhibitors (ACEIs), lisinopril has low lipophilicity and thus, theoretically, less propensity to cross the brain barriers than ramipril, which has high lipophilicity. The picture is further complicated by key differences in the protein binding, with lisinopril largely circulating as a free drug and ramipril been mostly bound to plasma proteins. Based on these considerations, lisinopril could entry the brain to a higher extent than ramipril. One of the most evident limitations in *Table 1* is the lack of data on CNS penetration for most of the molecules. In the only study published so far for ACEIs,[15] it was shown that cerebrospinal fluid (CSF) reached 4.1% (interquartile ranges 2.5–5%) of total serum concentrations for hydrochlorothiazide and 2.3% (1.7–5.7%) for ramiprilat, corresponding to about 11.3% and 5.5% of respective unbound serum concentrations. Since the CSF levels of these agents, both free and bound, were much lower than the corresponding concentrations in serum, the Authors concluded that the observed CNS adverse events were unlikely mediated primarily via direct effects of these drugs in the brain. These data suggest that the CNS concentrations reached by these antihypertensive drugs at therapeutic dosages are likely too low to carry out beneficial actions at a central level. Similarly, also for CCBs and diuretics, with a trend for higher CSF/plasma ratio reported for verapamil (7%) and diltiazem (10%) compared with bumetanide (2%).[16–18] Conversely, a significantly higher penetration has been reported for β blockers, ranging from 5% for propranolol up to 55% for bisoprolol.[15] This difference is presumably driven by a combination of high lipophilicity and low protein binding, with the exception of propranolol (*Table 1*).

3. Adrenergic modulators

3.1 Adrenergic receptors in the brain

Several antihypertensive drugs act through antagonism at β or α1, or agonism at α2 adrenergic receptors (*Table 2* and *Figure 2*). These adrenergic receptors are integrated in the Cortico-Striato-Thalamo-Cortical (CSTC) neurocircuitry,[19] where they regulate arousal, attention, anxiety, and emotional trauma through the norepinephrine signalling (among other neurotransmission systems). Although the adrenal medulla can release norepinephrine in the bloodstream, the locus coeruleus (LC) is the primary source of norepinephrine for the brain, since it innervates several areas of the cortex and can efficiently alter the CSTC function. The amount of released norepinephrine is proportional to the amount and intensity of stimuli received from sensory organs, and correlates directly with the overall activity of the CSTC. The norepinephrine receptors present in the CSTC circuit can be put in a

pharmacologically relevant order by decreasing affinity to norepinephrine, starting with the α2C presynaptic autoreceptors, α2A post-synaptic receptors and presynaptic hetero/autoreceptors, α1 post-synaptic receptors, and ending with β post-synaptic receptors: their sequential activation produces different cognitive effects, as detailed below.

During sleep, norepinephrine release from the LC is almost absent. During waking in the absence of stimuli, at the lowest norepinephrine concentrations, the presynaptic autoreceptors α2C on the LC noradrenergic neurones inhibit norepinephrine release towards the prefrontal cortex (PFC). As a consequence, the CSTC is in a resting condition. In the presence of external stimuli, low tonic norepinephrine release from the LC maintains wakefulness and allows the allocation of attention to distinct stimuli. In this context, the α2A post-synaptic receptors on the pyramidal neurones in the PFC lead to hyperpolarization-activated cyclic nucleotide-gated (HCN) channels closure and produce attention focussing. At the same time, the α2A presynaptic heteroreceptors on the serotoninergic neurones of the amygdala prevent emotional interferences, and the α2A presynaptic autoreceptors in the LC prevent further rises in norepinephrine release, thus maintaining a tonic signalling. In these circumstances, the CSTC directs attention towards salient stimuli.

Potent or repetitive sensorial stimuli produce a more intense and phasic norepinephrine signalling (rapid subsequent intense bursts), which engages α1 receptors. α1B receptors stimulation on PFC neurones[20,21] activates protein kinase C (PKC), which consecutively opens potassium channels SK and K_v7.[22,23] This leads to a reorientation of attention, which is not focussed anymore, but becomes diffuse and spatial (i.e. to look out for danger), while reducing the ability of the PFC to focus on specific tasks.[24] In this situation, corresponding to mild/acute stress, the CSTC engages memory formation, allowing emotional components to be included with the processing of sensory stimuli. α1A and α1D receptors in the hippocampus facilitate emotional memory formation.[25]

When very stressful conditions further enhance the noradrenergic signalling from LC, β adrenergic receptors are engaged and increase cAMP levels, thus triggering signalling and effects that are opposite to those of the α2A receptors in the PFC. The activation of β receptors in the PFC increases spatial arousal at the expense of attention and cognitive processing.[26] In addition, it stimulates serotoninergic neurones in the amygdala, favouring the adaptation to stress and promoting the formation of emotional memory.[27] In parallel, β receptors induce memory consolidation in the hippocampus,[28,29] with a specific preference for emotional events.[30,31] This mechanism is also involved in the development of emotional trauma and post-traumatic stress.

Other important and complex noradrenergic functions include the direct and indirect (via melatonin) regulation of sleep[32–34] and analgesia mediated by α2 receptors.[35]

3.2 Preclinical evidence for neuropsychiatric effects of adrenergic antihypertensive drugs and pharmacodynamic interactions with neuropsychiatric drugs

Based on their lipophilicity, noradrenergic antihypertensive drugs have different propensity to enter the brain and exert psychoactive effects (*Figure 1*). Attention and working memory can be enhanced by α2 agonists (including clonidine, guanfacine, methyldopa, guanabenz), α1 blockers (primarily the lipophilic prazosin), β blockers (mostly the lipophilic ones, without regard to β selectivity), and even more by α1/β blockers (carvedilol and labetalol). A possible side effect of these drugs is fatigue.[36] Further effects of α2 agonists include the reduction of anaesthetic and opioid dose requirements in the context of surgery.[37]

Regarding emotional associations and memory area, α1 blockers can prevent the formation of fear conditioning and stressful memories, but cannot revert them.[38] β1 blockers are acutely anxiolytic; however, they have delayed depressant effects, possibly due to the impairment of long-term potentiation. They induce symptoms of fatigue and lethargy, putatively due to their inhibitory activity on neuronal plasticity; they can alter sleep and cause nightmares in unclear ways; in rare cases, they can cause hallucination, possibly by disrupting dopaminergic signals.[28,29] Moreover, β blockers reduce melatonin levels.[39]

Concerning the interactions of antihypertensive drugs with neuropsychiatric drugs, secondary effect of α2 antagonism from α1 blockers can improve antidepressant action by avoiding some adverse effects that are due to norepinephrine and serotonin excess, in particular short-term anxiety and gastrointestinal disturbances.[40] Conversely, α2 antagonism can reduce the efficacy of several antipsychotics that work on the negative symptoms of schizophrenia and extrapyramidal disorders via serotonin increase. Lastly, α2 agonists can increase the adverse effects of antidepressants, while they can reduce the adverse effects and increase the therapeutic effects of antipsychotics.

α1 antagonism is a core mechanism by which antipsychotics reduce excessive arousal and reactive/aggressive behaviours; therefore, α1 blockers may improve the effectiveness of antipsychotics on soothing and sedation.

3.3 Clinical evidence for neuropsychiatric effects of adrenergic antihypertensive drugs and pharmacogenetic considerations

3.3.1 α2 agonists

Most of the recent evidence on the role of α2 agonists in psychiatry is on the rehabilitation treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in children.[41] Based on several large-scale randomized controlled trials (RCTs), the Food and Drug Administration (FDA) approved the extended-release formulations of clonidine and guanfacine, to treat children and adolescents aged 6– 17 years with ADHD. More recently, these drugs have been tested to treat a variety of psychiatric conditions beyond their approved indication. The main characteristics of studies reporting beneficial vs harmful effects of each antihypertensive drug class in the neuropsychiatric clinic are detailed in the Supplementary material online, *Table S1*. In adult ADHD patients, 3 RCTs showed that guanfacine produced clinically relevant improvements in core symptoms, executive function, and quality of life.[42–44] No data are available yet for clonidine in adults with ADHD.[45]

Clonidine and guanfacine showed other promising neuropsychiatric effects; however, these were reported in non-controlled studies and require verification in randomized blinded trials.

Regarding ADHD comorbidities, clonidine extended-release significantly improved symptoms of oppositional defiant disorder, conduct disorder, insomnia,[46,47] Tourette's syndrome, or tics in children with ADHD treated with stimulants.[48] Transdermal clonidine was used successfully to relieve anxiety and post-traumatic stress disorder (PTSD) symptoms in comorbidity with ADHD.[49–52] Guanfacine extended-release reduced intrusive thoughts and hyperarousal in children with PTSD.[53]

Other off-label use of clonidine includes the management of obsessive-compulsive disorder (OCD) symptoms[54] and clinically

Table 3 Beneficial vs harmful effects of adrenergic antihypertensive drugs in the neuropsychiatric clinic

Antihypertensive drug class	Possible therapeutic role (the investigated drug/class)	Harmful effects (the investigated drug/class)
Alpha 2 agonists[a]	Positive effects on: (i) core symptoms, executive function and quality of life in adults with ADHD (Guanfacine) [42–44] (ii) intrusive thoughts and hyperarousal in children with PTSD (Guanfacine)[53] (iii) oppositional defiant disorder, conduct disorder, insomnia, PTSD, Tourette's syndrome or tics in children with ADHD treated with stimulants (Clonidine)[46–53] (iv) hallucinations in adults with schizophraenia (Clonidine, in monotherapy)[56–58] (v) obsessive-compulsive disorder symptoms (Clonidine).[54]	Usually dose-related and reversible: dizziness, drowsiness, somnolence, and other depressive symptoms (All).[59,60] Manic reaction (guanfacine-extended release, up to 2 mg/day for 12 days).[59]
Alpha 1 blockers	Positive effects on: (i) PTSD symptoms, nightmares and sleep quality and content, both in adults[61–66] and children[67] (Prazosin) (ii) drug dreams in patients with substance use disorder (Prazosin).[68,69]	Not reported.
Beta blockers	Positive effects on: (i) anxiety in patients suffering from anxiety disorders (Propanolol)[70] (ii) aggression, verbal problem-solving/semantic fluency, working memory, social communication, in patients with schizophraenia, dementia, ASD (Particularly propanolol).[71–75]	Sleep disorders up to insomnia, nightmares, visual hallucinations, delirium or psychosis (All).[76–85]
Diuretics	Positive effects on: (i) ASD symptoms, in a limited subgroup of children who have a specific deficit in GABAergic circuits (Bumetanide)[86–91] (ii) CARS, ADOS, ABC, RDEG and RRB scores in a 10-year-old Fragile X boy (Bumetanide)[92] (iii) schizophraenia symptoms (Bumetanide, diazoxide).[93,94]	No clear neuropsychiatric effect would be expected of bumetanide.
CCBs	Positive effects on: (i) acute bipolar mania (All, particularly verapamil)[95,96] (ii) verbal memory, attention dysfunction and functional capacity in patients with schizophraenia (Isradipine)[97,98] (iii) cognitive function in elderly hypertensive people (All).[99,100]	Dizziness, difficulty sleeping and decreased energy in symptomatically-stable patients with schizophraenia (Isradipine).[97] Delirium in a 63-year-old man with ischaemic stroke (Amlodipine).[b]
ACEIs	Positive effects on: (i) depressed mood when compared with patients taking other antihypertensive drugs (All)[99,101–103] (ii) mental health outcomes (overall quality of life, positive wellbeing, mental and anxiety domains of quality of life) (All)[104] (iii) cognitive function in adult patients affected by cardiovascular disease (All).[b]	Visual hallucinations, paranoid delusions, confusion, disorientation, anxiety (Quinalapril).[b] A higher risk of major psychiatric disorders, compared to ARB users (adjusted HR = 1.07; 95% CI = 1.02, 1.13) (All).[b]
ARBs	Positive effects on: (i) schizophraenia symptoms (Telmisartan)[105,106] (ii) depression and anxiety and functional statuses (Valsartan)[b] (iii) cognitive function in older patients with hypertension (Candesartan).[107,108]	Risk for suicide (All).[109]

ABC, aberrant behaviour checklist; ADOS, autism diagnostic observation schedule; ARBs, angiotensin II type 1 receptor; ASD, autism spectrum disorder; CARS, Childhood Autism Rating Scale; GABA, gamma-aminobutyric acid; HR, hazard ratio; PTSD, post-traumatic stress disorder; RDEG, regulation disorder evaluation grid; RRB, repetitive and restrictive behaviour.
[a]Clonidine and guanfacine are approved treatment for ADHD in children, long-acting formulations only.
[b]The detailed list of references is reported in the Supplementary material online, *Table S1*.

relevant sleep problems in paediatric patients affected by neurodevelopmental disorders.[55] Clonidine has been also successfully used in monotherapy for hallucinations in adults with schizophrenia,[56–58] although its mechanism of antipsychotic effect remains hypothetical.

The most common psychiatric side effects due to the use of α2 agonists are usually dose-related and reversible, and include dizziness, drowsiness, somnolence, and other depressive symptoms.[59,60] Recently, a case of manic reaction in a child induced by guanfacine-extended release

(up to 2 mg/day for 12 days) was reported;[59] resolution occurred over 7 weeks following discontinuation of the α2 agonist. Clinical evidence on neuropsychiatric effects of antihypertensive drugs is briefly summarized in *Table 3*.

3.3.2 α1 blockers

A large amount of literature is available regarding the use of prazosin for sleep disturbances, specifically in the context of PTSD (see Supplementary material online, *Table S1*). The currently available systematic reviews and meta-analyses addressing adults have found predominantly positive findings on overall PTSD symptoms, nightmares, and sleep quality and content, supporting the use of prazosin as a good pharmacological option to treat PTSD.[61–65] However, prazosin was not effective in improving sleep disorders in patients with PTSD and alcohol dependence.[110] Although prazosin seems to be very promising in adults with PTSD, no firm conclusions should be drawn, due to the high methodological heterogeneity among studies on prazosin and PTSD, as well as the limited number of available trials.

A systematic review showed that prazosin may also be promising for PTSD-related nightmares in children and adolescents;[66] however, only sporadic case reports are currently available, supporting the need for well-designed placebo-controlled trials. Preliminary evidence supports the use of prazosin to treat 'drug dreams' in patients with substance use disorder.[68,69] Its mechanism of action seems to involve the decrease in noradrenaline effects at α1 adrenoreceptors, but is not well-characterized, particularly in the adolescent population.

Furthermore, preliminary studies have shown the potential efficacy of the α1-adrenergic antagonist doxazosin in the field of substance use disorder.[111,112] In these studies, doxazosin reduced cocaine use, presumably by modulating norepinephrine-mediated adrenergic effects and/or altering the balance of dopamine and norepinephrine.[71]A double-blind, randomized, placebo-controlled trial[113] found that cocaine use rates were influenced by the rs1611115 (c.-979T > C) polymorphism in the dopamine β-hydroxylase gene DβH, which codifies for the enzyme converting dopamine to norepinephrine). Cocaine use rates were lower in subjects with the T-allele (CT/TT) than in those with the CC genotype, with the T-allele associated with lower DβH and norepinephrine levels. The subsequent lower activation of α1 and β adrenergic receptors may result in reduced formation of emotional memory and reduced addiction mechanisms based on dopamine.

Another potential pharmacogenetic marker for substance use disorder was described in a 12-week placebo controlled clinical trial, focussed on the genetic variant rs2236554 (c.*129A > T) located in the intracellular domain of the α1 adrenoreceptor subtype D (ADRA1D) gene. In this trial, the T-allele carriers had a greater reduction of cocaine use after treatment with doxazosin.[114]

3.3.3 β blockers

According to specific properties related to their lipophilicity, intrinsic sympathomimetic activity, and cardioselectivity, β blockers may exert different therapeutic and adverse effects on the CNS.[115] It is well known that β blockers, especially propranolol and metoprolol, are associated with sleep disorders up to insomnia, nightmares, visual hallucinations, delirium or psychosis, even when they are used at low dose.[76–85]

Propranolol, the most investigated β blocker, showed potential for benefits in aggression, verbal problem-solving/semantic fluency,[71,72] working memory,[73] and social communication[74,75] in case series and single-dose studies on patients with a variety of neuropsychiatric conditions, such as schizophrenia, dementia, autism spectrum disorders (ASD), or behavioural disorders (see Supplementary material online, *Table S1*). A recent meta-analysis of RCTs found no evidence for effects of propranolol on PTSD symptom severity.[70]

Despite the wide range of potential psychiatric applications for β blockers, positive evidence is currently most robust for treating symptoms of social anxiety; further potential roles for β blockers include panic disorder, aggression in patients with psychosis, acquired brain injury or intellectual disability, and cognitive protection in patients with recent stroke (see Supplementary material online, *Table S1*).

RCTs suggest that some β-blockers may also have antidepressants effects.[116] Although more recent observational studies have challenged the association between β blocker therapy and increased risk of depression,[117,118] others have not.[119] Pharmacogenetic considerations tried to explain this discrepancy. Two common single nucleotide polymorphisms (SNPs) in linkage disequilibrium on the adrenergic β1 receptor (ADRB1) gene, p.Ser49Gly (rs1801252) and p.Gly389Arg (rs1801253), differentially affect blood pressure response to β-blocker therapy.[120,121] Noteworthy, the rs1801253 polymorphism of the β1 adrenergic receptor was associated also with a better response to antidepressant treatment in patients with major depression.[122,123] Furthermore, a study with homozygous 389Arg subjects examined the relationship between ADRB1 genetic variability and differences in systolic blood pressure and heart rate consequent to the use of SSRIs with high adrenergic β receptor affinity ('beta-blocking' SSRIs paroxetine and fluoxetine).[124] The study subjects receiving paroxetine and fluoxetine had significantly lower systolic blood pressure and heart rate than those receiving other SSRIs.[125] This evidence supports that ADRB1 genetic variability may also influence the effects of some antidepressants.

3.4 Adrenergic modulators—summary

The effects of adrenergic modulators depend on the receptor engaged in the brain. α1 antagonists reduce fear-related memories and enhance cognition even under stressful conditions; clinical data are however currently anecdotal and systematic research is needed to better elucidate their beneficial in treating patients with PTSD symptoms and substance use disorder. α2 agonists promote cognitive functions and potentiate antipsychotic effects, while increasing the adverse effects of antidepressants. α2 antagonists reduce the adverse effects of antidepressants, but decrease the efficacy of antipsychotics. Lastly, β antagonists, which are anxiolytic, induce symptoms of depression, including fatigue and lethargy, and sleep disruption. As most evidence on the role of β blockers comes from case reports and observational studies, rigorous studies investigating their benefits are needed.

4. Diuretics

4.1 Receptors for diuretics in the brain

Diuretic drugs act on molecular targets that are class-specific or even drug-specific. Diuretics alter the electrolyte content and, consequently, the excitability of neurones, thus producing changes in neurotransmission and potential neuropsychiatric effects. Diuretics have very different neuropsychiatric profiles depending on which receptor they engage.

Thiazide diuretics act predominantly by inhibiting sodium/chloride co-transporters; some of them can also inhibit the activity of several carbonic anhydrase (CA) subtypes (*Figure 2*). Sodium/chloride co-transporters participate in regulating the concentration of electrolytes throughout the body; they are crucial for neuronal activity and for the pharmacokinetics of any drug.

Among potassium sparing diuretics, amiloride and triamterene have their main target in the epithelial sodium channel (ENaC) (*Figure 2*), which is in the same superfamily as acid sensing ion channels (ASICs). ENaCs are ubiquitous, while ASICs are enriched in neurones and have important roles still under investigation.[126]

Spironolactone is a highly lipophilic mineralocorticoid antagonist with minor action on the androgen receptor, and a much less potent antagonist of the oestrogen and glucocorticoid receptors. The loop diuretics furosemide and bumetanide act by inhibiting the sodium-potassium-chloride co-transporter NKCC2; they also target its isoform NKCC1, expressed in the juvenile brain, which becomes increasingly silenced with neuronal development.[127] As long as NKCC1 expression is high, the chloride electrochemical potential inside neurones is high. Consequently, GABA-triggered chloride currents flow inside-out and GABA acts as an excitatory neurotransmitter. This mechanism is considered important for brain synchronization and synapse wiring during brain development stages. Later, the electrochemical potential of chloride generates by the potassium-chloride co-transporter KCC2, which orients GABA-triggered chloride currents outside-in and allows the inhibitory activity of GABA that is typical of adult neurones.[128]

4.2 Preclinical evidence for neuropsychiatric effects of diuretic antihypertensive drugs and pharmacodynamic interactions with neuropsychiatric drugs

All diuretics may cause whole-body electrolyte imbalances, thus resulting in various neurological adverse effects and/or in altered pharmacokinetics of psychoactive drugs. A neuropsychiatric effect of thiazides is not known. Moreover, the lipophilic metolazone might alter electrolyte levels in the brain more efficiently than other non-lipophilic thiazides. The role of CAs has been increasingly studied with respect to synaptic function, spatial learning, memory,[129] and altering the function of GABA receptor channels. Some lipophilic thiazides (indapamide, metolazone) may contrast seizures through their inhibitory action on CAs, similarly to some antiepileptic drugs that inhibit CAs (e.g. acetazolamide, methazolamide, zonisamide, and topiramate).[130] CAs functionality is required for proper cognitive and memory processes, whereas insufficient CA activity may be connected with risk of dementia.[131] CA1 was found to be either down-regulated or up-regulated in depression.[132,133] Moreover, the antidepressant drugs fluoxetine, sertraline, and citalopram were shown to activate CA1 and CA2,[129] whereas the CA1 inhibitor acetazolamide was suggested to be useful in treating the depressive phase of bipolar disorders.[134] Antipsychotic drugs also inhibit CA1 and CA2,[67] with an unknown functional role.

Among potassium sparing diuretics, amiloride and triamterene are scantly lipophilic. Therefore, at therapeutic dosages, these drugs would unlikely reach significant concentrations in the brain. There is ongoing research with respect to intranasal administrations of amiloride, which should reach the brain more efficiently, but its effects are yet to be defined.[135]

Mineralocorticoid receptors are not currently associated with any neuropsychiatric effect. However, several observations suggest that they are involved in neurogenesis aspects that establish anxious responses to stress.[136] Furthermore, a decreased response to mineralocorticoid agonists has been found in depression, indicating down-regulation of the mineralocorticoid receptors.[137] Mineralocorticoid receptors may also take part in addictive behaviours with unclear roles.[138] Moreover, mineralocorticoid receptors have been shown to inhibit non-transcriptionally the NRG1-ERBB4 pathway, which is involved in the cognitive symptoms of schizophrenia:[139] indeed, spironolactone is being tested as add-on treatment in schizophrenic patients with cognitive impairments.[140]

The possible role of NKCC1 dysregulation in the aetiopathogenesis of several neuropsychiatric disorders has been investigated. NKCC1 may be a promising target for the treatment of specific epilepsies,[141,142] neurodevelopmental disorders including autism spectrum disorders and tuberous sclerosis, and neuropsychiatric disorders including schizophrenia, anxiety, pain, and brain degeneration or injury.[143,144] The therapeutic relevance of treatments based on NKCC1 channels is yet to be proven, also because the correlation between bioavailability in the brain and neuropsychiatric effects is unclear. Furosemide is the most lipophilic NKCC1 blocker and also inhibits the CA; however, it found scarce application. The hydrophilic bumetanide, which reaches the brain to a very limited extent (<1% brain/plasma concentration),[145] has been extensively tested for autism spectrum disorders, infantile seizures, and other disorders.[10] Bumetanide may be efficacious for a subset of autistic patients, while it fails to improve symptoms in the average population; its antiepileptic role is harshly contested.[146] Part of the scepticism around bumetanide depends on its scant permeability to the brain; therefore, several optimization approaches have been applied. One bumetanide lipophilic prodrug, its dimethylaminoethyl ester (BMU5), showed promising results in increasing the seizure threshold after epileptogenic brain insults.[147,148] However, BUM5 decreased survival in a mouse model of stroke, probably due to toxic effects following accumulation in the brain upon several days of administration.[149] More recently, the potential anticonvulsant efficacy of the lipophilic bumetanide derivative BUM97 was assessed in *in vivo* models.[150] The treatment suppressed hippocampal paroxysmal discharges and spike trains in a dose-dependent manner; moreover, it exerted a synergistic anticonvulsant effect with phenobarbital.

4.3 Clinical evidence for neuropsychiatric effects of diuretics

Most of the existing data on the role of diuretics in psychiatry are related to the use of bumetanide for treating core symptoms of ASD.[86–91] Following a pilot study,[151] 2 placebo-controlled randomized trials tested bumetanide in paediatric patients with ASD.[152,153] In both trials, bumetanide reduced measures of core autism symptoms significantly. Additional anecdotal evidence came from studies on emotion recognition[154,155] and reports of single cases of success, for instance in a boy with Fragile X.[92] Phase 2 trials suggested further efficacy of bumetanide on repetitive behaviours, but no effects on other outcomes of social responsiveness. Phase 3 international trials failed to show significant effect of bumetanide over placebo on any outcome in the latest interim analyses, thus leading to a disappointing stop in drug development.[156] Despite this positive evidence on the role of bumetanide in treating children with ASD, it must be considered that autism is not a homogeneous psychiatric condition.[157,158] Some sporadic positive evidence on the role of bumetanide and diazoxide in treating schizophrenia has been reported;[93,94] however, further research is needed to investigate this hypothesis.

4.4 Diuretics—summary

CA-inhibiting lipophilic thiazides may have neuropsychiatric effects on mood and cognition, yet to be thoroughly investigated in preclinical

models. Agonism at the NKCC1 receptor is the only mechanism currently targeted in clinical applications for the treatment of autism spectrum disorders and epilepsy of specific aetiology. Thus, the use of bumetanide is limited to subpopulations of patients.[159] It remains to be clarified how the hydrophilic bumetanide can be more efficacious than the lipophilic furosemide, how it could be better targeted, and whether conditions other than a subset of autism spectrum disorders may be treated with NKCC1 inhibitors. Furthermore, as for future applications, CA inhibitors are being studied as antiepileptic agents, and spironolactone is being studied for addiction and/or schizophrenia. Except for pharmacokinetic effects based on volaemic changes, no interactions with neuropsychiatric drugs are known or expected from diuretics.

5. Calcium channel blockers

5.1 L-type calcium channels in the brain

CCBs inhibit the inward current of Ca^{2+} ions by binding to the L-type 'long-acting' voltage-gated Ca^{2+} channels (LTCCs). These react to membrane potential depolarization by opening, thereby allowing Ca^{2+} to pass into the cytosol[160] (*Figure 2*). Cytosolic Ca^{2+} can modulate signalling pathways either directly, by binding Ca^{2+}-dependent kinases and phosphatases, or indirectly, via the Ca^{2+} binding protein calmodulin.[161] As LTCCs activity in the brain is connected with neuropsychiatric functions, CCBs might have therapeutic potential.

The LTCCs consist of the α1 subunit, that forms the pore, and of the additional α2δ, β, and γ subunits.[162] Four different genes (CACNA1S, CACNA1C, CACNA1D, CACNA1F) encode for the α1 subunits of the channel isoforms (Cav1.1-Cav1.4), differing in their biophysical properties, pharmacological specificities, and locations.[162] The auxiliary subunits play a role in channel membrane localization, activity, and dynamic regulation.[163,164] All isoforms of LTCCs are sensitive to the main classes of CCBs (dihydropyridines [DHPs], phenylalkylamines, and benzothiazepines), but differ in terms of tissue distribution and gating activity.[165] The brain isoforms of LTCCs are Cav1.2 and Cav1.3. These are expressed especially in the hippocampus, amygdala, and substantia nigra, though at a different extent (approximately 90% Cav1.2 and 10% Cav1.3).[166,167] Initial pharmacological assessments, complemented by studies in genetic animal models, have dissected the role of the Cav1.2 and Cav1.3 isoforms in synaptic plasticity and learning and memory processes in CA1 pyramidal neurones in the hippocampus.[168] These studies showed the specific involvement of Cav1.2 in the consolidation or reconsolidation of spatial memory.[169,170] Cav1.3 is implicated in the neuronal plasticity and in the age-dependent cognitive decline by allowing the Ca^{2+} influx underlying the slow post-burst after-hyperpolarization (AHP).[171] Moreover, Cav1.3 is involved in processes regulating the formation of fear memories within the lateral amygdala.[172,173] Cav1.2 and Cav1.3 channels contribute to modulate the dopaminergic mesoaccumbens pathway, which regulates natural reward sensitivity and behavioural processes underlying drug addiction.[174] Furthermore, they both are expressed by microglia and appear to play a role in neuroinflammation by triggering secretion of inflammatory signals.[175]

5.2 Preclinical evidence for neuropsychiatric effects of CCBs and pharmacodynamic interactions with neuropsychiatric drugs

Despite the structural differences among the three classes, all the CCBs reversibly bind the α1 subunit of the LTCCs and interfere with the voltage-dependent activation of the channel.[160] Since Cav1.2 and Cav1.3 channels have very similar pharmacological properties, CCBs discriminate between these channels only weakly.[160,166] However, the analysis of the binding of different dihydropyridines to both channels suggested some selectivity for Cav1.2 of nifedipine and nitrendipine.[160,176]

The data obtained by the genetic modification of brain LTCCs suggest behavioural effects and anxiolytic-like features for CCBs, which are possibly related to the modulation of neurotransmitters release.[177,178] Preclinical *in vitro* and *in vivo* data showed that CCBs modulate the activity of Cav1.2 and Cav1.3 channels in the brain. However, evidence in hypertensive patients suggests that therapeutic doses of these drugs do not affect brain function.[167] Nevertheless, these data help understand the mechanism of action of the channels and the therapeutic potential of their inhibitions. In a study carried out in mice that had been treated with CCBs acutely, verapamil and diltiazem facilitated depression, presumably through an off-target decrease of the release in norepinephrine and serotonin at higher dosages. Conversely, nifedipine showed an antidepressant-like behaviour,[178] in line with a previous paper reporting an antidepressant profile for nifedipine and other DPHs, such as nicardipine, nitrendipine, isradipine, felodipine, and nimodipine. The involvement of the LTCCs in this event was further confirmed by the finding that an activator of the channels, Bay K8644, reduced the effect of nifedipine.[179] *In vivo*, nimodipine reduced fear conditioning, an animal model of fear and anxiety, by significantly depressing neurotransmitters release and excitatory post-synaptic currents (EPSC) in the amygdala.[180] Recently, it has been reported that diltiazem produces anxiolytic-like effects in mice via the up-regulation of brain neurosteroids, such as tetrahydrodeoxycorticosterone and allopregnanolone.[181] Blocking LTCCs with isradipine in organotypic slices and mouse models of neurotoxin-induced Parkinson's disease showed neuroprotection of dopaminergic neurones, probably by inhibiting mitochondrial oxidative stress increase.[182,183]

Noteworthy, CCBs may interact pharmacodynamically with diverse psychoactive drugs. Up-regulation of LTCCs has been reported in rat brain after repeated administration of psychostimulant drugs such as methamphetamine, cocaine, and opioids (e.g. morphine).[184] However, the concurrent administration of nimodipine prevented the up-regulation of the channels caused by opioid administration.[185] In general, in preclinical studies, CCBs prevented or reduced important components of dependence and the development of tolerance, presumably by acting at the level of mesolimbic dopamine system on neuronal transmission and synaptic plasticity.[186] Moreover, it has been recently reported that acute administration of the SSRI fluoxetine reduces the morphine-induced up-regulation of Cav1.2 and Cav1.3 in cortex and mesolimbic; moreover, when administered along with either nimodipine or diltiazem, fluoxetine increases morphine-induced anti-nociception.[187]

5.3 Clinical evidence for neuropsychiatric effects of CCBs and pharmacogenetic considerations

CCBs have been studied clinically in psychiatric conditions such as mood disorders and substance abuse/dependence, yielding conflicting results (see Supplementary material online, *Table S1*). Isradipine was effective in improving schizophrenia symptoms in two recent RCTs;[97,98] however, no clear evidence of a role of CCBs in neurocognition is currently available.[99,100]

Interestingly, genome-wide association studies (GWAS) support a role for the gene codifying for the main target of antihypertensive

CCBs, CACNA1C, in bipolar disorders, major depressive disorders, schizophrenia, and ASD.[188–193] Moreover, variants in CACNA1C have been correlated with sleep latency and sleep quality by GWAS.[194,195] In a Mendelian randomization study, genetically predicted insomnia was associated with a higher hypertension risk.[196] Several SNPs in CACNA1C have been linked to psychiatric disorders, with most of them being located in a large intron between exons 3 and 4 (intron 3).[197] Many studies have been performed on the SNP rs1006737 in CACNA1C. There is a significant association of this polymorphism with bipolar disorders, major depressive disorders, schizophrenia, and ADHD. At molecular level, rs100637 is correlated with changes in CACNA1C expression and an increased L-type current in induced human neurones derived from individuals carrying rs1006737.[198] Furthermore, the minor allele for rs1006737 (A) is correlated with increased methylation of CpG islands located within intron 3.[199] Imaging studies have shown associations of rs1006737 with changes in structure and activity of brain regions that are related to emotion processing, memory formation, and cognition.[200,201] The effect of the rs1006737 genotype and its interaction with LTCC antagonism could be clarified by the Oxford study of Calcium channel Antagonism, Cognition, Mood instability and Sleep (OxCaMS), an exploratory experimental medicine study of the LTCC antagonist nicardipine given to participants with high mood instability.[202]

To date, observational studies have reported contradictory associations between CCBs intake and mood disorders (see Supplementary material online, *Table S1*). In a longitudinal study based on a large hospital database of patients hospitalized for mood disorders, the use of CCBs and β blockers was associated with an increased risk of admission for mood disorders.[101] Conversely, in a cohort study of patients with serious mental illness, reduced rates of psychiatric hospitalization and self-harm were observed in patients with bipolar disorder and schizophrenia who were treated with CBBs.[203] Two recent systematic reviews of studies investigating the role of CCBs in bipolar disorder showed no evidence of superiority of verapamil over placebo in treating acute mania.[95,96] Based on genetic associations between voltage-gated calcium channels and major depression, CCBs have been associated with decreased risk of developing depression in a few uncontrolled clinical trials.[197,204]

5.4 CCBs—summary

CCBs interact with the brain isoforms of LTCCs Cav1.2 and Cav1.3, thereby modulating their channel activity. The preclinical evidence suggests that CCBs might have therapeutic value in the treatment of neuropsychiatric disorders, neurodegenerative diseases, and drug dependence. However, human clinical studies are not conclusive about an association between CCBs intake and mood disorders therapy. This might be due to a low CFS drug concentration at the dosage used for cardiovascular disease treatment.

6. Renin-angiotensin system modulators

6.1 Renin-angiotensin system in the brain

Two renin-angiotensin systems (RAS) exist in the brain, the systemic and the local RAS.[205,206] However, since the BBB restricts the access of the systemic RAS components to most brain regions, the brain RAS is probably essential in the pathophysiology of several neurodegenerative diseases.[207–209] The brain RAS plays also an important role in regulating autonomic functions and maintaining cardiovascular homeostasis.[210] The enzyme renin initiates the RAS pathway by producing angiotensin I (Ang I) through the cleavage of angiotensinogen. Within the brain, renin has been found within neurones and astrocytes,[211] while angiotensinogen is mainly produced and secreted by astrocytes.[211–213] Four neuroactive peptides derive from Ang I: Ang II, Ang IV, Ang (1–7), and alamandine. The angiotensin converting enzyme (ACE) cleaves Ang I to generate Ang II, which is the principal effector peptide of RAS and binds two different receptors, the Ang II type I receptor (AT1R) and the type II receptor (AT2R). Ang I and Ang II may generate Ang III, an intermediate peptide that engages AT1R and AT2R and can be further processed to Ang IV. The latter binds Ang II type IV receptor (AT4R) and at high concentration also AT1R. In addition, Ang I or II can be cleaved by the isoform ACE2 to produce Ang (1–7), which binds Mas receptor (MasRs).[214] Alamandine, an analogue of Ang (1–7), is the most recently discovered peptide of the RAS system; it functions through the interaction with the Mas-related-G protein coupled receptor (MrgD).

AT1Rs, AT2Rs, and MasRs are G-protein coupled receptors (GPCRs) located on neurones, astrocytes and microglia of the cortex, hippocampus, and basal ganglia;[215,216] MrgDs and AT4Rs have been found only in neurones.[217–219] The up-regulation of ACE expression and the increased activation of AT1R signalling exacerbate inflammation, cell death, and cognitive impairment.[215,220,221] On the contrary, AT2Rs, AT4R, MasRs, MrgDs, and ACE2 have antioxidant and anti-inflammatory activity and stimulate cell survival and cognition.[215,222,223] Neurones, microglia, and astrocytes express AT1Rs and AT2Rs, both at the plasma membrane level and intracellularly, especially in the mitochondria and nuclei.[213,223,224]

Neurones can produce an intracellular form of renin and secrete the precursor form of renin, prorenin; both can bind to prorenin receptors (PRRs), which are also expressed in neurones and lead to angiotensinogen cleavage.[213]

The binding of Ang II to the neuronal plasma membrane AT1R leads to the recruitment of heterotrimeric G proteins (Gq/G11 and/or Gi/Go) and/or adaptor proteins such as JAK2, GRK2, and β-arrestin. This triggers different intracellular pathways such as the production of reactive oxygen species (ROS) via the activation of the NADPH oxidase (NOX).[225,226] The increase of oxidative stress is also a consequence of the activation of NOX4 via the mitochondrial AT1R; this pathway exacerbates cell death in the cortex, hippocampus, and basal ganglia, which are essential for cognitive functions.[224,227]

Nuclear AT1R, however, induces AT2R expression that functions in an opposite way to AT1R/ACE signalling. Plasma membrane AT2R regulates neuronal excitability and differentiation, and promotes neurite outgrowth and cell survival through the activation of multiple pathways.[228–232] In mitochondria, AT2R modulates mitochondrial respiration to decrease ROS production.[228] AT1R and AT2R are almost undetectable in microglia of healthy brain, while they are up-regulated in activated cells in pathological conditions related to inflammation.[220] Up-regulation of AT1R exacerbates neuronal damage through the activation of NOX signalling and ROS production.[233] Conversely, the increased expression of AT2R appears to be a compensatory mechanism involved in the switch of microglial cells toward an anti-inflammatory phenotype that blunts ROS production via NOX inhibition.[234]

AT1R activation in astrocytes has both negative and positive outcomes. In neurones and microglia, it leads to the increase of ROS generation via the NOX pathway, to oxidative stress, and to cell death. However, AT1R activation decreases the permeability and maintenance

of the BBB through the mobilization of occludin, a protein of the tight junctions, in the lipid rafts of the brain endothelial cell.[227,235]

Regarding the role of brain RAS in hypertension, accumulating evidence indicates that RAS constituents and mediators of inflammation act on the brain within a neural network to increase the sympathetic nervous system activity and, consequently, blood pressure.[236,237] Furthermore, the increase of Ang II in the brain appears to be one of the compensatory responses of neuro-humoral activation during the development of chronic heart failure.[238]

The brain RAS modulates also sensory information processing, learning and memory, and emotional responses.[239] Ang II induces dopamine and serotonin release when infused in the rat brain via presynaptic AT1R stimulation.[240,241] RAS may also promote cell survival by modulating the brain levels of the brain-derived neurotrophic factor (BDNF) and its receptor tropomyosin-related kinase B receptor (TRKB) through the activation of AT2R.[242,243] The hyper-activation of the brain RAS has been involved in the pathogenesis of several neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, depression, schizophrenia, and bipolar disorder.[244] In particular, the pathogenesis of depression and bipolar disorder is linked to hyper-activation of the hypothalamic–pituitary–adrenocortical (HPA) axis:[245,246] under stress conditions, the increase of Ang II and the activation of AT1R induce gene expression and release of the corticotropin-releasing hormone by the neurosecretory cells in the paraventricular nucleus of the hypothalamus (PVN), thereby triggering the entire cascade of the HPA axis.[247] A role for RAS in schizophrenia has been hypothesized[248,249] based on different lines of evidence, such as: *i.* changes in the levels of ACE in the brain of patients affected by schizophrenia;[250] *ii.* the involvement of brain RAS in glutamate-induced oxidative stress and in dopaminergic vulnerability;[227,251,252] *iii.* the positive effects of AT2R activation in neurite outgrowth and elongation, neuronal excitability, and synapse plasticity;[228–232] *iv.* the capability of ACE to cleave peptides such as neurotensin and substance P, which are dysregulated in schizophrenia patients, the former being associated with regulation of dopamine transmission and the latter with neuroinflammation.[253–255]

6.2 Preclinical evidence for neuropsychiatric effects of modulation of renin-angiotensin system in the brain

Drugs targeting the RAS at various levels, such as ACEIs, ARBs, and renin inhibitors, are used to treat cardiovascular diseases.[256,257] Evidence supporting the antidepressant effects of these drugs is increasing. In a recent study in mice, the ACEI captopril and lisinopril showed a rapid and long-lasting beneficial effect on stress-induced depressive-like behaviours.[258] However, this event was mediated not by a direct action on the RAS, but by potentiating a pathway involving bradykinin, a secondary substrate of ACE, and the mammalian target of rapamycin complex 1 (mTORC1).[258] Moreover, captopril reduced anxiety behaviour, as did candesartan and losartan, while enalapril did not show any neuropsychiatric effect.[259–261] Similarly, valsartan, irbesartan, and telmisartan exerted an antidepressant effect, indicating that AT1R stimulation is involved in controlling the cognitive and behavioural responses to stress and anxiety.[262–264]

The beneficial effect of pharmacological modulation of RAS in schizophrenia mainly depends on the neuroprotective properties of ARBs. Regarding treatment of schizophrenia-related cognitive impairment with irbesartan, losartan, and telmisartan, a novel mechanism of action has been hypothesized, which involves the negative regulation of the kynurenine aminotransferase II and the reduction of kynurenic acid.[265] Indeed, high levels of kynurenic acid in the brain are associated with memory impairment and psychotic symptoms.[266] Furthermore, the high lipophilic telmisartan is particularly interesting among ARBs as a central modulator in schizophrenia, as it showed the strongest anti-inflammatory activity and the highest affinity for PPAR-γ, which is increased in patients with schizophrenia.[267] In a mouse model of schizophrenia at peri-pubertal age, candesartan was administered at a dosage below the starting dose used to treat hypertension in children and adolescents. It prevented behavioural alterations with a mechanism that appeared to be independent of AT1R activation and presumably consistent with a direct antioxidant effect of the molecule.[268,269]

6.3 Clinical evidence for neuropsychiatric effects of renin-angiotensin-system acting agents and pharmacogenetic considerations

Although it has been reported that ACEIs have positive effects on mood when compared with patients taking other antihypertensive drugs,[99,101–103] there is scant evidence on the use of ACEIs in the field of neuropsychiatry (see Supplementary material online, *Table S1*). Associations between ACE polymorphisms and depression have been described,[270,271] and altered methylation of the regulatory region of the ACE gene has been reported in depression.[272] A great body of evidence suggested that ACE insertion (I)/deletion (D) polymorphism (rs4646994) (ACE I/D) may be associated with depression;[273] moreover, this polymorphism presumably plays a role in the modulation of serotonergic and dopaminergic turnover in the human CNS.[274] In addition, the SNP rs4291, which is located in the promoter region of the ACE gene and influences ACE activity and HPA-axis hyperactivity, was associated with unipolar major depression.[273] In a case-control study including 961 individuals[102] and in a subsequent study using Danish nationwide population-based registers,[103] clinical evidence confirmed that ACEIs were associated with a decreased rate of onset of depression.

Genetic studies[275,276] have identified an association between the ACE I/D polymorphism (rs4646994) and schizophrenia; however, the findings are contradictory. The first case-control study showed that the II genotype of the I/D polymorphism had a protective effect for schizophrenia among females, whereas there was no significant association between I/D polymorphism and susceptibility to schizophrenia among male subjects.[275] Conversely, a meta-analysis found no association between the ACE I/D polymorphism and schizophrenia.[276] Similarly, inconsistent findings have been reported for ACE activity and protein levels with regard to schizophrenia.[248,277] In a study, ACE activity was decreased in the plasma of patients with schizophrenia compared with healthy controls; however, it was increased in another study. The Schizophrenia Working Group of the Psychiatric Genetics Consortium[278] published a preprint of the largest GWAS of schizophrenia, which included 69 369 cases and 236 642 controls. Using fine-mapping and functional genomic data, the authors prioritized 19 genes based on protein-coding or UTR variation, including the well-known candidate CACNA1C. Furthermore, through a summary-based Mendelian randomization analysis, they showed an association of decreased ACE expression in blood with increased risk of schizophrenia. This analysis parallel with the findings of another Mendelian randomization study that suggested an association of lower levels of ACE (messenger RNA and protein) with decreased systolic blood pressure (SBP) on one side, and with an increased risk of schizophrenia on the other side.[279] There was no evidence for an association between genetically

estimated SBP and schizophrenia risk, suggesting that any association of ACE with schizophrenia is presumably independent of its association with blood pressure.

Beside major depressive disorder, SNPs within the ACE gene were also significantly associated with acute stress response and higher mortality following a major trauma.[273,280,281] In particular, the rs4311 SNP within the ACE gene, that has been associated with the panic attack syndrome, might be a functional polymorphism that increases risk for dysregulated fear responses.[282] In a cohort study recruiting trauma-exposed individual, this polymorphism was associated with PTSD symptoms and diagnosis, as the T-carriers at the rs4311 SNP had significantly greater likelihood of a PTSD diagnosis.[283]

A large meta-analysis suggested that the insertion (I)-deletion (D) polymorphism of the ACE gene could be a marker of Alzheimer's disease (AD).[284] In particular, the D allele was associated with raised plasma levels of the enzyme,[285] and the genotype DD was protective for AD risk;[284] conversely, the presence of the I allele was associated with an increased risk of AD.[286,287] This association could be due to linkage disequilibrium with the true risk factor. A very recent study supposed that the effects of the ACE insertion/deletion polymorphism might differ according to the apolipoprotein E ϵ4 (APOE*4) carrier status, the only fully established susceptibility allele for AD.[288]

With regard to ARBs, data in humans are currently very limited. Clinical reports and observational studies recently reported encouraging findings in psychotic patients;[105,106] protective effects of ARBs on cognition,[107,108] depression, and anxiety have also been reported (see Supplementary material online, *Table S1*). According to recent findings from a meta-analysis of 11 RCTs comparing ACEIs or ARBs versus either placebo or non-ACEI or non-ARBs, the use of ACEI or ARBs was significantly associated with improved mental health domains in adults (overall quality of life, positive wellbeing, mental and anxiety domains of quality of life).[104]

Noteworthy, in a recent 12-week randomized, double-blind, placebo-controlled study, the adjunctive treatment with telmisartan improved schizophrenia symptoms in 22 patients receiving either clozapine or olanzapine.[106] However, no adjustments were made for multiple comparisons; moreover, due to the limited duration of the trial and the small simple size, no firm conclusion can be drawn. In a nested case-control study investigating all antihypertensive drug classes, suicide risk was associated only with ARB use (OR: 3.52; 95% CI: 1.33–9.30).[109]

6.4 Renin-angiotensin system modulators—summary

Increasing preclinical evidence supports the antidepressant and antipsychotic effects of drugs targeting the RAS. Particularly interesting are ARBs, with their neuroprotective properties exerted through the stimulation of AT1R and its downstream pathways. The psychotropic potential of these medications is supported by studies demonstrating a genetic association between ACE polymorphisms and depression/schizophrenia. The available clinical evidence further points to a psychotropic role of RAS modulators. However, the intrinsic limitations of the studies that have addressed the topic (e.g. small cohort size, observational nature, small period of observation) support the need for further trials with larger sample sizes and longer treatment durations. Such studies should aim to characterize the beneficial effects of RAS-acting agents on psychopathology, cognition, and safety in patients with schizophrenia and mood disorders, along with the potential mechanism mediating these effects and pharmacogenetic aspects.[249]

7. Other antihypertensive drugs

7.1 Vasodilators

The blood vessel dilating drugs hydralazine and minoxidil have important off-target activities in the brain that do not involve vasodilation; however, since preclinical and clinical evidence is scant, we only provide a summary of the available data.

The hydrophilic drug hydralazine is thought to act as an antioxidant by preventing the degradation of NO and thereby increasing its activity. Hydralazine can also inhibit inositol-triphosphate channels, which control calcium release from intracellular storages. Calcium concentrations in the neurone participate in controlling survival, structural, and functional aspects, which are connected also with memory and neurodegeneration.[289–291] A therapeutic role for hydralazine is currently only hypothetical; furthermore, its high hydrophilicity and intense antihypertensive effect may prevent the possibility to reach useful concentrations in the brain.

Minoxidil is a lipophilic opener of ATP-sensitive potassium channels (K_{ATP}), which can trigger the relaxation of blood vessels smooth muscles and play a crucial role in peripheral and hypothalamic glycaemic regulation. Beside these roles, K_{ATP} channels can couple the electrical activity of neurones with a check of energy availability, possibly playing a role in brain injury following ischaemia or hypoxia. Indeed, K_{ATP} channels dysfunction has been putatively connected with neurodegeneration, in particular of dopaminergic neurones.[292] Minoxidil hypothetically plays a role in neuroprotection following toxic damage or ischaemia, as shown in cardiomyocytes,[293,294] but no studies have been conducted on patients yet.

7.2 Reserpine

Reserpine is a lipophilic monoamine depleting agent that irreversibly inhibits the vesicular monoamine transporter (VMAT), which reuptakes norepinephrine, serotonin, and dopamine from the cytosol into presynaptic vesicles (*Figure 2*). The consequent increase in the cytosolic concentration of monoamines leads to their degradation by monoamine oxidase and to depletion. Subsequently, monoamines have to be synthesized anew. This action of reserpine is depressant. In addition, reserpine may also induce neurone loss, due to an increased energy expenditure for neurotransmitter synthesis. Indeed, there are pathological models of pain, depression, and neurodegeneration induced by reserpine treatment.[295,296] There are scant observations of neuropsychiatric effects of reserpine in clinical practice or clinical trials.

8. Conclusion and perspectives

Preclinical studies have explored the molecular mechanisms through which antihypertensive drugs lead to neuropsychiatric effects; however, clinical data are currently insufficient to recommend the use of most antihypertensive drugs based on possible beneficial/harmful effects in selected psychiatric comorbid patients. Notable exceptions are lipophilic noradrenergic antihypertensive drugs, which cause symptoms attributable to depression, and bumetanide, which may obtain a therapeutic placement for autism or epilepsy in specific patients. When treating psychiatric comorbid patients, knowledge of the neuropsychiatric mechanisms of action and effects of antihypertensive drugs can help discriminate between psychiatric comorbidity and the adverse effects (or unexpected positive effects) that may occur.

Overall, the effects of adrenergic modulators depend on the engaged receptors. α2 agonists, recently approved for the treatment of ADHD, promote cognitive functions and potentiate antipsychotic effects, while increasing the adverse effects of antidepressants. They relieve anxiety and PTSD symptoms, and show beneficial effects in the management of OCD and schizophrenia. α1 antagonists reduce fear-related memories and enhance cognition, even under stressful conditions. Prazosin, thanks to its anxiolytic effect, is used to treat PTSD by reducing the overall burden of disease symptoms. Similarly, β antagonists show a potential benefit in schizophrenia, anxiety, ASD, and behaviour disorders, but induce symptoms of depression, including fatigue and lethargy, and sleep disruption, thereby reducing the efficacy of some antidepressant medications. Limited data are available on the effects of diuretic drugs in the field of neuropsychiatry. The inhibition/antagonism of NKCC1 receptor is the only mechanism currently targeted in clinical applications for the treatment of ASD and epilepsy of specific aetiology, limiting their use to specific subpopulations of patients. For future applications, clinical studies have been exploring the potential use of CA inhibitors as antiepileptic agents and of spironolactone for treatment of addiction and/or schizophrenia.

CCBs are associated with a relative low rate of psychiatric complications, but also with a poor positive effect on brain function. Under debate is their potential role in improving or worsening cognitive functions and mood disorders. CCBs seem to reduce psychiatric hospitalization in patients with schizophrenia, whereas no evidence supports their role to improve acute mania and bipolar disorders, or an antidepressant effect. Evidence of neuropsychiatric effects of drugs targeting RAS is currently almost absent. However, ACEIs and ARBs rescue anxiety- and depression-like phenotypes in animal models, and seem to improve mental health and schizophrenia symptoms in human.

Open questions regard on the one hand how to avoid undesirable effects or interactions with neuropsychiatric drugs and, on the other hand, how to exploit these additional mechanisms for neuropsychiatric treatment. Adverse effects can be avoided by switching drugs, for instance to a less lipophilic equivalent, or by choosing the proper combination between antihypertensive and neuropsychiatric drugs to avoid undesired interactions. Therapeutic development of antihypertensive drugs can be pursued firstly by solving the bioavailability issue, since most have limited penetration in the CNS. There are three different approaches to improve the pharmacological profile of these drugs. One is to use lipophilic prodrugs that more easily penetrate the brain barriers and are subsequently metabolized, once within the CNS, to release the active moieties. The second approach is to design lipophilic derivatives of antihypertensive drugs that cross the brain barriers more easily than the parent compound. The third is to modify those antihypertensive drugs that have different targets in the CNS, reducing their antihypertensive potential that may be excessive or untoward when considering neuropsychiatric applications.

Future studies should include outcomes of neuropsychiatric interest, because previous studies have focussed on cardiovascular outcomes and only reported anecdotal evidence on neuropsychiatric aspects. The Mendelian randomization approach may provide an additional piece of evidence about the effects of drugs on certain neurological diseases, especially since RCTs are sometimes too expensive or even impossible to perform. Some studies have already applied this approach to investigate the effects of antihypertensive drugs in the context of neuropsychiatric diseases.[297–299]

Supplementary material

Supplementary material is available at *Cardiovascular Research* online.

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Data availability

Data derived from sources in the public domain. Reference details are provided in full (both in the Main text and in the Supplementary Material online).

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