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# Original mechanisms of antipsychotic action by the indole alkaloid alstonine (*Picralima nitida*)

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ABSTRACT

Alstonine is the major component of plant based remedies that traditional psychiatrists use in Nigeria. Alstonine is an indole alkaloid that has an antipsychotic experimental profile comparable with that of clozapine and is compatible with the alleged effects in mental patients. Representing a desirable innovation in the pharmacodynamics of antipsychotic medications, the evidence indicates that alstonine does not bind to $D_2$ dopamine receptors (D2R) and differentially regulates dopamine in the cortical and limbic areas. The purpose of this study was to further investigate the effects of alstonine on D2R binding in specific brain regions using quantitative autoradiography (QAR) and its effects on dopamine (DA) uptake in mouse striatal synaptosomes. The effects of alstonine on D2R binding were determined in the nucleus accumbens and caudate-putamen using QAR in mice treated with alstonine doses that have antipsychotic effects. The effects of alstonine [3H]DA uptake were assessed in synaptosomes prepared from striatal tissue obtained from mice treated acutely or for 7 days with alstonine. Alstonine did not change the D2R binding densities in the studied regions. DA uptake was increased after acute (but not after 7 days) treatment with alstonine. Consistent with the alstonine behavioral profile, these results indicate that alstonine indirectly modulates DA receptors, specifically by modulating DA uptake. This unique mechanism for DA transmission modulation contributes to the antipsychotic-like effects of alstonine and is compatible with its behavioral profile in mice and alleged effects in patients. These results may represent an innovation in the antipsychotic development field.



## Introduction

Schizophrenia, with a 1% estimated global prevalence, is a serious highly debilitating psychiatric disorder, and the currently available treatments lack adequate efficacy, particularly regarding negative and cognitive symptoms (Dolgin 2014). Considered to be the result of a complex interplay between genetic and environmental factors (Modinos et al. 2013), schizophrenia is thought to include dopaminergic imbalance (Kuepper et al. 2012); whereas hypoactive cortical dopaminergic regions lead to negative (e.g., social interaction withdrawal and affective flattening) and cognitive (e.g., attention and memory deficits) symptoms, hyperactive mesolimbic dopaminergic pathways correlate to positive (e.g., delusions and hallucinations) symptoms. There are two classes of antipsychotics: typical (older) agents basically act via dopamine $D_2$ receptor (D2R) antagonism, and atypical (newer) agents generally act through various receptors (including $5HT_{2A}$, $5HT_{1A}$, $5HT_{2B}$ and $D_3$) (Meltzer 2013). Despite these differences, the D2R antagonism (or partial agonism) is considered essential to produce antipsychotic effects. The development of new drugs with better results on cognitive and negative symptom is critical for improving the treatment of people with schizophrenia (Ellenbroek 2012).

Due to their structural similarity with tryptophan, indole alkaloids have historically been associated with the development of central nervous system-acting drugs. Physiostigmine, strychnine, ergotamine and psyloscibine are well known examples of such drugs. In the context of this study, reserpine, an indole alkaloid isolated

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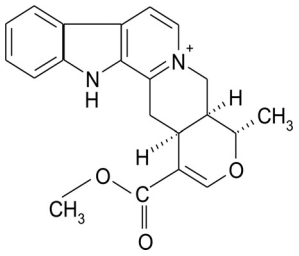

**Fig. 1.** Structure of the indole alkaloid alstonine.

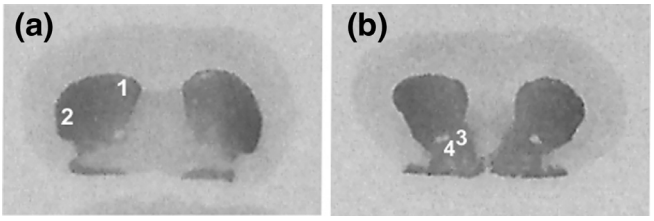


**Fig. 2.** Representative images from [3H]nemonapride QAR. Mouse brain regions areas analyzed: (1) medial CPu; (2) lateral CPu; (3) NAc shell; (4) NAc core.

from *Rauwolfia serpentina* Benth., is considered the first antipsychotic medication to have been discovered in modern times. Alstonine is an indole alkaloid (Fig. 1) that has been identified as the major component of a plant based remedy used by Igbo traditional psychiatrists (Costa-Campos et al. 1999). In addition to its traditional use for treating mentally ill patients, alstonine has an experimental profile comparable with those of atypical agents in mice models of positive (Costa-Campos et al. 1998), negative (de Moura Linck et al. 2008) and cognitive (Linck et al. 2012) schizophrenia symptoms. Although the alstonine mechanism of action has not been fully clarified, behavioral and neurochemical data suggest it is not a D2R antagonist (Costa-Campos et al. 1998). As with atypical antipsychotics, the data indicate the involvement of the serotonergic $5HT_{2A}$ and $5HT_{2C}$ receptors (Linck et al. 2012) and decreased glutamate uptake (Herrmann et al. 2012) as part of its mechanism of action.

If proven, the apparent lack of D2R blockade by alstonine would represent an innovative pharmacodynamic basis for antipsychotic properties. The aim of the present study is to further investigate the alstonine mechanism of action by analyzing its effects on D2R binding in relevant brain areas (through quantitative autoradiography) and dopamine uptake by striatal synaptosomes.

## Methods

### *Animals*

Male (CF1) 2-month-old adult albino mice (40–45 g) were used in this study. Mice were maintained in the animal facility under controlled environmental conditions (22 ± 1 °C, 12-h light/dark cycle, free access to food and water) for at least 2 weeks before the experiments. This study was approved by the University Ethics Committee (#18236); all procedures were performed in accordance with institutional policies on experimental animal handling.

### *Drugs*

1,3-Ditolylguanidine (DTG), clozapine, GBR12909, pargyline and dopamine were purchased from Sigma Chemical Co. (St. Louis, MO, USA); sulpiride, cis-flupentixol and pindolol from Research Biochemicals International (Natick, MA, USA). [$^3$H]dopamine (38.7 Ci/mmol) and [$^3$H]nemonapride (YM-09151-2, 85.5 Ci/mmol) were purchased form Perkin Elmer Life Sciences (Boston, MA, USA). Clozapine, sulpiride and pindolol were solubilized in HCl (1N), and the pH adjusted to 6.0 with 1 N NaOH; DTG was solubilized in methanol; all other drugs (including alstonine) were solubilized in distilled water and prepared freshly before use. Treatments were administered intraperitoneally (0.1 ml/10 g of body weight).

*Alstonine Isolation and Identification:* Alstonine (hydrochloride) was isolated from the rinds of *Picralima nitida* (Stapf) T. Durand & H. Durand (Apocynaceae) fruit. The separations used pH-zone-refining counter-current chromatography as previously described (Okunji et al. 2005). Briefly, the experiment was performed using a two-phase solvent system composed of methyl tert-butyl ether (MtBE)–acetonitrile–water (2:2:3, v/v); triethylamine (TEA) was added to the upper organic stationary phase as the retainer, and hydrochloric acid (HCl) was added to the aqueous mobile phase as the elution reagent. The sample was prepared by dissolving 15.0 g of the alkaloid fraction obtained from the methylene chloride extract of *P. nitida* in 100 ml of a phase mixture comprising equal volumes of each phase. The separation was initiated by loading the sample into a column that was completely filled with the stationary phase (LC pump); the mobile phase was pumped into the CCC column at a rate of 2 ml/min while the column was rotated at 834 rev/min using the combined head in tail elution mode. The absorbance of the eluate was continuously monitored at 280 nm, and 4 ml fractions were collected. The pH of each eluted fraction was determined using a pH meter, and fractions were dried using a Speed Vac. The pH-zone refining CCC pure fractions were identified using thermospray liquid chromatography–mass spectrometry (LC–MS) and in TLC co-elution experiments using reference alstonine samples provided by InterCEDD, Nsukka, Nigeria. The purity of the alstonine sample used in this study was 98%, and the identity was confirmed by HPLC–MS.

### *$D_2$-like receptors quantitative autoradiography*

The protocol used for these experiments was modified from Berger et al. (2002). Naïve mice were sacrificed, and the whole brains were quickly removed, immediately frozen by immersion in Freon (15–20 s) and stored at −80 °C. Cryostat sections (Leica CM18-50, Leica Microsystems Nussloch GmbH, Germany) that were 12 $\mu$m thick were thawed-mounted onto gelatin-coated microscope slides and dried on a warm plate for 30 s. Six sections were mounted per slide, which were desiccated with silica and stored at −80 °C. Coronal brain sections obtained transected the caudate-putamen (CPu) and nucleus accumbens (NAc) according to Fraklin and Paxinos (2007). The sections were preincubated at room temperature for 1 h in 50 mM Tris–HCl buffer (pH 7.4) containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, and 1 mM $MgCl_2$ and further incubated for 1 h in the same buffer with added clozapine (10 or 100 $\mu$M) or alstonine (10 or 100 $\mu$M) plus 1.0 nM [3H]nemonapride, 0.5 mM DTG, and 0.1 mM pindolol (to block sigma ($\sigma$1,2) and 5HT1A sites, respectively). Nonspecific binding was determined using 40 $\mu$M sulpiride. After the incubations, the sections were rinsed twice in Tris–HCl buffer (4 °C, 5 min) and dipped (3x) in cold distilled water. The sections were dried under a stream of air, briefly placed on a warm plate (60 °C, 60 s) and cooled to room temperature before film exposure. Radioactivity standards (American Radiolabeled Chemical Inc.) consisting of 14 sections of methacrilate plastic impregnated with tritium (0.14–489 $\mu$Ci/g) were jointly exposed with the sections. The autoradiograms were obtained after 30 days (−4 °C) exposure in light-tight cassettes to Kodak Professional D-19 (Sigma) film and developed in Kodak Dektol (Sigma Chemical Co., St. Louis, MO, USA) developer and fixative. Autoradiography images were scanned in a conventional scanner (600 dpi), relevant brain regions were outlined (Fig. 2) and the analyses were performed using the Image J software (http://rsb.info.nih.gov/nih-image/). Optical density was converted to nCi/mg of tissue using calibrated methacrylate tritium standards; after subtracting nonspecific (15–22%) from total binding, specific binding was expressed as fmol/mg tissue.

*Dopamine uptake*

Synaptosomal preparations were obtained from acute or subchronic treated mice. In the acute treatment, mice were treated with saline, clozapine (2.0 mg/kg) or alstonine (0.5 or 1.0 mg/kg) and sacrificed 30 min later; in the subchronic treatment, mice received the same treatments daily for 7 days and were sacrificed 24 h after the last administration.

[$^3$H] Dopamine uptake was determined in rat striatal synaptosomal preparations based on the method detailed by Fleckenstein et al. (1999) and Pandolfo et al. (2011). Briefly, synaptosomes were prepared by homogenizing mouse striatal fresh tissue in ice-cold Tris buffer (0.32 M sucrose, 1 nM EDTA and 0.25 nM DTT; pH 7.4), followed by centrifugation (1000 *g*/10 min/4 °C). Supernatants (S1) were centrifuged at 17,000 *g* for 20 min at 4 °C; the resulting pellets (P2) were re-suspended in assay buffer (in mM: 126 NaCl, 4.8 KCl, 1.3 CaCl, 1.4 $MgSO_4$, 11 glucose, 1.1 ascorbic acid, 16 sodium phosphate; pH 7.4) and centrifuged (17,000 *g*/10 min/4 °C) to completely remove residual sucrose. The final P2 pellets were re-suspended in ice-cold assay buffer. Aliquots of striatal synaptosomes (50 $\mu$l) were warmed for 4 min at 37 °C and incubated for 5 min at 37 °C in glass test-tubes (500 $\mu$l final incubation volume) with 500 nM dopamine (0.09 $\mu$Ci/ml [$^3$H]dopamine was used as trace with unlabeled dopamine) and 1 $\mu$M pargyline (to prevent dopamine metabolization by MAO). Incubations were terminated by adding 2 ml of ice-cold assay buffer, followed by vacuum filtration through glass microfiber filters (Whatman GF/B). The filters were washed twice with 3 ml ice-cold 0.32 M sucrose, dried for 10 min at 60 °C and placed in scintillation vials containing 1.5 ml scintillation liquid. Radioactivity was measured using a scintillation counter (2800TR TriCarb Liquid Scintillation Analyzer, Perkin Elmer – Waltham, MA, USA). Synaptosome protein content was measured as described by Bradford (1976), using bovine serum albumin (BSA) as a standard. Dopamine uptake was converted into pmol DA/min/mg protein and expressed as % of control. All experiments were performed in triplicate.

Demonstrating that dopamine was mainly transported by DAT, pilot experiments determined that the selective DAT inhibitor GBR 12909 (1 $\mu$M) inhibited dopamine uptake by 89.3% in these preparations (data not shown). Here, 50 $\mu$M unlabeled dopamine resulted in 89.9% inhibition, indicating that there was 11% non-specific uptake (data not shown). The non-specific uptake was determined for each synaptosomal preparation (using 50 $\mu$M unlabeled DA).

*Statistics*

Data were analyzed using one-way ANOVA followed by the Newman–Keuls post hoc test using GraphPad Prism 5 for Windows; $p < 0.05$ was set as the threshold for statistical significance.

## Results

*D2R quantitative autoradiography*

Clozapine (10 and 100 μM) significantly decreased [$^3$H] nemonapride binding in the CPu and NAc (medial CPu $F_{(4,20)} = 41.1$; lateral CPu $F_{(4,19)} = 72.2$; NAc core $F_{(4,19)} = 65.6$; NAc shell $F_{(4,19)} = 39.9$; $p < 0.01$) (Fig. 3). Alstonine (10 and 100 μM) did not modify [$^3$H]nemonapride binding.

*Dopamine uptake*

Acute treatment with 1.0 mg/kg (but not 0.5 mg/kg) alstonine increased synaptosomal dopamine uptake ($F_{(3,32)} = 3.2$; $p < 0.05$, Fig. 4a). Clozapine treatment did not significantly affect synaptosomal dopamine uptake (Fig. 4a). Subchronic treatment with alstonine or clozapine did not modify dopamine uptake ($F_{(3,33)} = 0.3$; $p > 0.05$) (Fig. 4b).

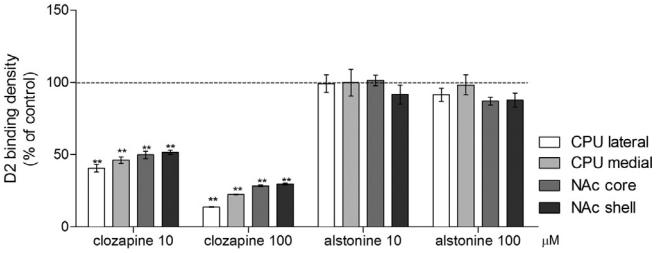


**Fig. 3.** Effects of clozapine and alstonine on [$^3$H]nemonapride binding density. Data are represented as % of control mean ± S.E.M. ∗= $p < 0.05$; ∗∗= $p < 0.01$ compared with the control group (dotted line), ANOVA/SNK ($n = 3$–5).

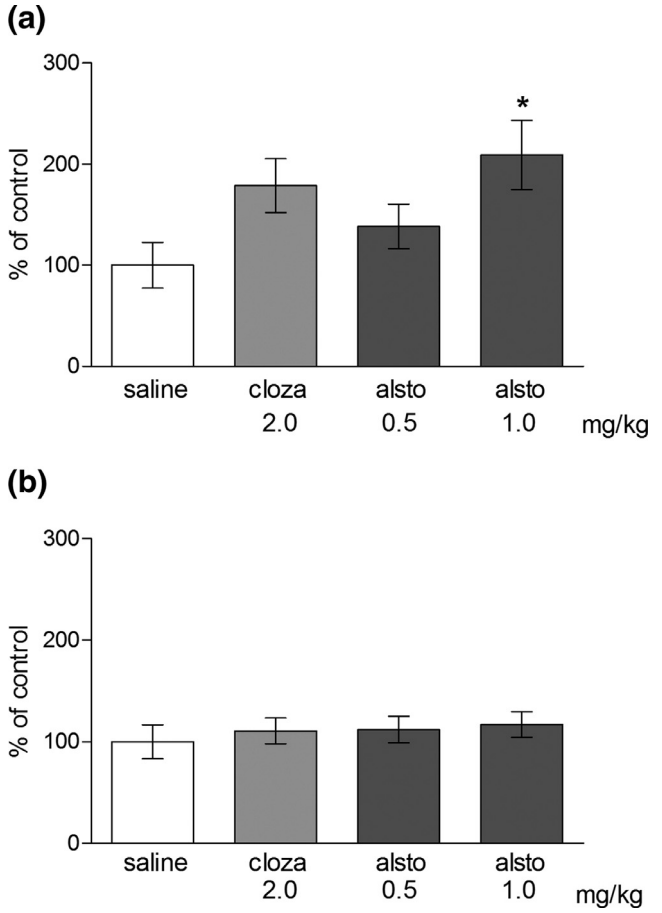


**Fig. 4.** Effects of (a) acute and (b) sub-chronic treatment with clozapine (Cloza) and alstonine (Alsto) on mouse striatal synaptosomal DA uptake ($n = 8$–10). Data are expressed as % control. ∗ = $p < 0.05$ compared with control (Ctrl) or saline group, ANOVA/SNK.

## Discussion

The data obtained in this study corroborate our previous hypothesis that alstonine does not bind to D2R because the QAR data clearly demonstrate that alstonine does not bind to D2R. In addition to the lack of D2R binding in striatal membrane preparations (Costa-Campos et al. 1998) and the lack of changes in prolactin levels (Linck et al. 2011), the absence of D2R binding, now better characterized using QAR data, can be considered an important differential aspect of alstonine as an antipsychotic drug. D2R is abundant in the NAc and CPu brain areas, which are relevant for positive schizophrenia symptoms and antipsychotic side effects, respectively. The QAR method was used to simultaneously examine the effects of alstonine in several relevant and small brain regions, i.e., the NAc core and shell.

Another important finding in this study is that in mice treated with alstonine, there was a two-fold increase in striatal DA uptake, which is

correlated with the dose and timing of the antipsychotic-like effects of alstonine in mice models of positive symptoms (Costa-Campos et al. 1998). Increasing DA synaptic uptake represents a novel mechanism for decreasing dopamine transmission, which could ultimately regulate the purported hyperactive mesolimbic dopamine. The increasing effects of alstonine on DA uptake are not observed after chronic 7-day treatment; because the DA levels are normal in experimental animals, such a compensatory mechanism is to be expected. The results of long-term alstonine administration are likely to differ in the context of hyperactive DA pathways, such as in the brains of people with schizophrenia.

There are approximately 40 different antipsychotics on the market, all of which block D2R to some extent (Insel 2010; Ellenbroek 2012). The consistent antipsychotic profile of alstonine in mice, as well as the therapeutic outcomes alleged by traditional Nigerian psychiatrists, requires that the mechanism of dopamine pathway modulation be clarified. Although other antipsychotic-like compounds lacking D2R binding are under development (such as mGluR2/3 ligands, $\alpha 7$ nicotine agonists and 5-HT6 antagonists) (Ellenbroek 2012), to the best of our knowledge, this is the first report of an antipsychotic-like compound that modulates DA uptake. The increase in DA uptake reported here coincides with the observed increased DOPAC (intraneuronal DA metabolite) levels in the striatum of mice acutely treated with the same doses of alstonine (Linck et al. 2011).

The DAT transporter has been a proposed target for developing new antipsychotics (Runyon and Carroll 2006). As the primary mechanism responsible for regulating DA availability at the non-cortical synaptic cleft (Leviel 2011; Runyon and Carroll 2006), DAT plays key roles in cognition, affect, behavioral reinforcement and motor function (Gainetdinov and Caron 2003; Volz and Schenk 2005). The DAT density (in rodents and humans) is lower in the frontal cortex, where noradrenaline transporter (NET) and catechol-O-methyltransferase (COMT) are responsible for DA inactivation (Morón et al. 2002). Due to this differential DAT distribution, alstonine-induced increases in dopamine uptake would be particularly relevant for decreasing DA levels in non-cortical synapses but would have little impact in cortical areas. Given the cortical/mesolimbic imbalance in DA function in schizophrenia (Abi-Dargham 2004), a differential modulation of dopamine function in the cortex and mesolimbic areas is desirable for an optimal antipsychotic medication (Correll 2011). Increasing DA uptake may be an adequate mechanism for attenuating schizophrenia dopamine hyperactivity, possibly without the unwanted side effects associated with the direct blockade of dopamine receptors.

Notably, reserpine irreversibly blocks the vesicular monoamine transporter (VMAT2), and there is evidence that reserpine also inhibits DAT (Metzger et al. 2002). Alstonine is present in *Rauwolfia* species such as *Rauwolfia caffra* Sond. and *Rauwolfia vomitoria* Afzel. (Elisabetsky and Costa-Campos, 2006) and shares the same biosynthetic pathway as reserpine. For this reason, these two alkaloids have some structural similarities that may be relevant to their effects on monoamine transporters. Since the discovery of reserpine, antipsychotics have ameliorated the quality of life of schizophrenia patients (Duval and Goldman 2000), although the cognitive and negative symptoms are, unfortunately, little improved (Dolgin 2014). Due to the complexity of schizophrenia neurobiology, multiple-target drugs are expected to possess a better antipsychotic profile (Kim and Stahl 2010). In addition to the participation of $5HT_{2A/C}$ serotonin receptors (Linck et al. 2012) and glutamate (Herrmann et al. 2012) in the antipsychotic-like effects of alstonine, this study indicates the neurochemical mechanism by which dopamine transmission modulation contributes to the antipsychotic profile of alstonine.

## Conflict of interest

The authors have no conflicts of interest to declare.

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## References

Abi-Dargham, A., 2004. Do we still believe in the dopamine hypothesis? New data bring new evidence. Int. J. Neuropsychopharmacol. 7 (Suppl. 1), S1–S5.
Berger, M.A., Barros, V.G., Sarchi, M.I., Tarazi, F.I., Antonelli, M.C., 2002. Long-term effects of prenatal stress on dopamine and glutamate receptors in adult rat brain. Neurochem. Res. 27, 1525–1533.
Bradford, M.M., 1976. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. Anal. Biochem. 72, 248–254.
Correll, C.U., 2011. What are we looking for in new antipsychotics. J. Clin. Psychiatry 72 (Suppl. 1), 9–13.
Costa-Campos, L., Elisabetsky, E., Lara, D.R., Carlson, T.J., King, S.R., Ubillas, R., Nunes, D.S., Iwu, M.M., Nkemjika, C.O., Ozioko, A., Agwu, C.O., 1999. Antipsychotic profile of alstonine: ethnopharmacology of a traditional Nigerian botanical remedy. An Acad. Bras. Cienc. 71, 189–201.
Costa-Campos, L., Lara, D.R., Nunes, D.S., Elisabetsky, E., 1998. Antipsychotic-like profile of alstonine. Pharmacol. Biochem. Behav. 60, 133–141.
de Moura Linck, V., Herrmann, A.P., Goerck, G.C., Iwu, M.M., Okunji, C.O., Leal, M.B., Elisabetsky, E., 2008. The putative antipsychotic alstonine reverses social interaction withdrawal in mice. Prog. Neuropsychopharmacol. Biol. Psychiatry 32, 1449–1452.
Dolgin, E., 2014. Therapeutics: negative feedback. Nature 508, S10–S11.
Duval, A.M., Goldman, D., 2000. The new drugs (chlorpromazine & reserpine): administrative aspects, 1956. Psychiatr. Serv. 51, 327–331.
Elisabetsky, E., Costa-Campos, L., 2006. The alkaloid alstonine: a review of its pharmacological properties. Evid. Based Complement. Alternat. Med. 3, 39–48.
Ellenbroek, B.A., 2012. Psychopharmacological treatment of schizophrenia: what do we have, and what could we get. Neuropharmacology 62, 1371–1380.
Fleckenstein, A.E., Haughey, H.M., Metzger, R.R., Kokoshka, J.M., Riddle, E.L., Hanson, J.E., Gibb, J.W., Hanson, G.R., 1999. Differential effects of psychostimulants and related agents on dopaminergic and serotonergic transporter function. Eur. J. Pharmacol. 382, 45–49.
Fraklin, K.B.J., Paxinos, G., 2007. The Mouse Brain in Stereotaxic Coordinates. Elsevier Inc..
Gainetdinov, R.R., Caron, M.G., 2003. Monoamine transporters: from genes to behavior. Annu. Rev. Pharmacol. Toxicol. 43, 261–284.
Herrmann, A.P., Lunardi, P., Pilz, L.K., Tramontina, A.C., Linck, V.M., Okunji, C.O., Gonçalves, C.A., Elisabetsky, E., 2012. Effects of the putative antipsychotic alstonine on glutamate uptake in acute hippocampal slices. Neurochem. Int. 61, 1144–1150.
Kim, D.H., Stahl, S.M., 2010. Antipsychotic drug development. Curr. Top. Behav. Neurosci. 4, 123–139.
Kuepper, R., Skinbjerg, M., Abi-Dargham, A., 2012. The dopamine dysfunction in schizophrenia revisited: new insights into topography and course. Handb. Exp. Pharmacol., 1–26.
Leviel, V., 2011. Dopamine release mediated by the dopamine transporter, facts and consequences. J. Neurochem. 118, 475–489.
Linck, V.M., Bessa, M.M., Herrmann, A.P., Iwu, M.M., Okunji, C.O., Elisabetsky, E., 2012. 5-HT2A/C receptors mediate the antipsychotic-like effects of alstonine. Prog. Neuropsychopharmacol. Biol. Psychiatry 36, 29–33.
Linck, V.M., Herrmann, A.P., Piato, A.L., Detanico, B.C., Figueiró, M., Flório, J., Iwu, M.M., Okunji, C.O., Leal, M.B., Elisabetsky, E., 2011. Alstonine as an antipsychotic: effects on brain amines and metabolic changes. Evid. Based Complement. Alternat. Med. 2011, 1–7.
Meltzer, H.Y., 2013. Update on typical and atypical antipsychotic drugs. Annu. Rev. Med. 64, 393–406.
Metzger, R.R., Brown, J.M., Sandoval, V., Rau, K.S., Elwan, M.A., Miller, G.W., Hanson, G.R., Fleckenstein, A.E., 2002. Inhibitory effect of reserpine on dopamine transporter function. Eur. J. Pharmacol. 456, 39–43.
Modinos, G., Iyegbe, C., Prata, D., Rivera, M., Kempton, M.J., Valmaggia, L.R., Sham, P.C., van Os, J., McGuire, P., 2013. Molecular genetic gene-environment studies using candidate genes in schizophrenia: a systematic review. Schizophr. Res. 150, 356–365.
Morón, J.A., Brockington, A., Wise, R.A., Rocha, B.A., Hope, B.T., 2002. Dopamine uptake through the norepinephrine transporter in brain regions with low levels of the dopamine transporter: evidence from knock-out mouse lines. J. Neurosci. 22, 389–395.
Okunji, C.O., Iwu, M.M., Ito, Y., 2005. Preparative separation of indole alkaloids from the rind of Picralima nitida (Stapf) T. Durand & H. Durand by pH-Zone-refining countercurrent chromatography. J. Liq. Chromatogr. Rel. Technol. 28, 775–783.
Pandolfo, P., Silveirinha, V., dos Santos-Rodrigues, A., Venance, L., Ledent, C., Takahashi, R.N., Cunha, R.A., Köfalvi, A., 2011. Cannabinoids inhibit the synaptic uptake of adenosine and dopamine in the rat and mouse striatum. Eur. J. Pharmacol. 655, 38–45.
Runyon, S.P., Carroll, F.I., 2006. Dopamine transporter ligands: recent developments and therapeutic potential. Curr. Top. Med. Chem. 6, 1825–1843.
Volz, T.J., Schenk, J.O., 2005. A comprehensive atlas of the topography of functional groups of the dopamine transporter. Synapse 58, 72–94.