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The molecular interaction between the glutamatergic, noradrenergic, dopaminergic and serotoninergic systems informs a detailed genetic perspective on depressive phenotypes

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ABSTRACT

The glutamatergic pathway has been consistently involved in the physiopathology of depressive disorder. However a complete dissection and integration of its role in the context of other known mechanisms is lacking. We summarized and integrated the evidence of various levels of interaction between glutamatergic and monoaminergic pathways (see videos). We identified six molecular pathways, some of which with specific regional distribution within the brain. From the six pathways we identified the key proteins and their coding genes, we then provided a detailed list of possible candidates with practical suggestions for association studies planning.

Contents

Abbreviations: 5-HT, serotonin; 5-HT1A, 5-HT receptor 1A; 5-HT1B, 5-HT receptor 1B; 5-HT2A, 5-HT receptor 2A; 5-HT6, 5-HT receptor 6; ABP, AMPAR-binding protein; AIF, apoptosis-inducing factor; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionate; Arc, cytoskeletal-associated protein; CaM, calmodulin; CaMKII, Ca^{2+}/calmodulin-dependent protein kinases or CaM kinases; CREB, cAMP response element binding protein; DA D1, dopamine receptor D1; DA D2, dopamine receptor D2; DA D4, dopamine receptor D4; DA, dopamine; DAG, diacylglycerol; DISC1, disrupted-in-schizophrenia 1; EAAT, excitatory amino acid transporters; ERK, extracellular signal regulated kinases; GABA, gamma-aminobutyric acid; GPCRs, G protein-coupled receptors; GRIP, glutamate receptor interacting protein; GWAS, genome wide analyses studies; IDO, indoleamine 2,3-dioxygenase; iGluRs, ionotropic glutamate receptors; KA, kainate; LTDP, long term depotentiation; LTP, long term potentiation; MAP kinase, mitogene activated protein kinase; MDD, major depressive disorder; mGluRs, metabotropic glutamate receptors; NE, norepinephrine; NFL, neurofilaments; NMDA, N-methyl-D-aspartate; nNOS, nitric oxide synthase; NSF, N-ethylmaleimide-sensitive fusion protein; PAG, phosphate activated glutaminase; PARS, poly(ADP-ribose) synthase; PDE, phosphodiesterase; PI, polyphosphoinositide; PICK1, protein interacting with C alpha kinase 1; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; PLC, phospholipase C; PP1, protein phosphatase 1; PSD-95, postsynaptic density 95; SAP97, synapse-associated protein 97; SERT, serotonin transporter; sGC, soluble guanylate cyclase; SNARE, soluble N-ethylmaleimide-sensitive factor attachment receptor; SYN, synaptophysin; TCA, tricarboxylic acid cycle; VGLUT, vesicular glutamate transporters; CNS, central nervous system.

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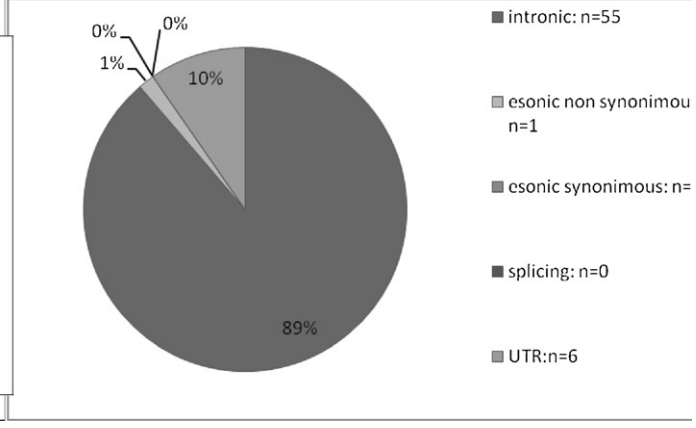
1. Introduction

In the present review we reorganize the evidence on the biological underpinnings of MDD by focusing on the monoaminergic and the glutamatergic theories. The monoaminergic theory asserts that an imbalance in monoamines (serotonin (5-HT), dopamine (DA) and norepinephrine (NE) mainly) leads to MDD. The glutamatergic theory posits that the glutamate may shape the risk of depression influencing the neuronal fate (neurotoxicity) or the unfolding of new neuronal nets (neuroplasticity). The monoaminergic theory dominated the field for the last decades and part of the current antidepressant pharmacological treatments are inspired by it (Nutt, 2006). Nonetheless, monoamine depletion does not cause MDD in healthy subjects (Ruhe et al., 2007), suggesting that something else may act unseen. The glutamatergic system may done part to this concealed molecular mechanism (Krystal et al., 2002; Skolnick et al., 2009), probably through a complex and constant influence towards the monoaminergic systems. Supporting this, substances with glutamatergic properties have antidepressant effects (Trullas and Skolnick, 1990; Skolnick et al., 2009), some antidepressant treatments lead to the down regulation of the glycine B site (glycine is a modulator of the glutamatergic function) and of the NMDA (a glutamatergic receptor type) (reviewed in Krystal et al., 2002), the antidepressant tianeptine is a modulator of the glutamatergic function (McEwen et al., 2010) and ketamine (which acts through inhibiting NMDA receptors) reverses the behavioral and physiological alterations induced by chronic mild stress in rats, and has been proved to be an antidepressant in humans (Berman et al., 2000; Goforth and Holsinger, 2007; Kudoh et al., 2002; Zarate et al., 2006). In particular, a new generation of antidepressant molecules may emerge in the next future that will target a specific subtype of NMDA receptor, the NR2B. A recent complete review can be found at (Skolnick et al., 2009). Moreover, the antidepressant effects of the glutamatergic drugs can be explained by a monoaminergic mechanism: the down regulation of the adrenergic receptors or the enhancement of the serotoninergic function are associated with the administration of the glutamatergic antidepressant substances (Lejeune et al., 1994; Martin et al., 1998; Pallotta et al., 1998; Wedzony et al., 1997). Consistently, the chronic treatment with antidepressants causes a reduction of glutamate release (Tokarski et al., 2008). Starting from this, we delineate the molecular boundaries between the monoaminergic and glutamatergic systems, we then describe the main metabolic cascades that mediate MDD on the basis of the monoaminergic–glutamatergic interplay and we eventually identify the genetic variations that best describe these molecular cascades. This set of variations is the final output of the present work (Table 1, Arnold et al., 2006; Barton et al., 2004; Brookes et al., 2005; Dickel et al., 2006; Dong et al., 2009; Gadow et

Table 1
Selection and representation of the SNPs for the candidate genes that best describe the candidate molecular paths (see text). In this table some critical genetic information are shown that help the definition of the best investigational strategy for every single candidate (last line in the first square for each line). The number of validated variations for each gene is provided, the corresponding number of tagging variations and the number of variations that are tagged by the former ones. A graphical representation is provided in the right column of the table. Coverage when all the validated variations are forced in the analysis is also provided, in order to show how much of the gene is covered by the tagging approach at the highest of its potential. On the basis of this result, the best strategy (tagging versus functional) is selected. Functional variations include esonic synonimous, non synonimous, variations that impact the splicing and variations located in the regulatory regions. Finally, the best candidates retrieved for each gene on the basis of its peculiarities is provided in the box at the center of every line in the table.

Gene	VALIDATED	TAGGING_HAP_MAP	TAGGED_HAP_MAP	% OF COVERAGE	% COVERAGE WHEN SNP ARE FORCED IN	GRAPHICAL REPRESENTATION (BASED ON NCBI)
CREB1	56	4	19	33.9	33.9	

name: cAMP responsive element binding protein 1
position: 2q33.3
length: 75,824 bases
evidence in literature: (Dong *et al.*, 2009; Hettema *et al.*, 2009; Laje *et al.*, 2009; Liu *et al.*, 2010; Serretti *et al.*, ahead of print)
proposed investigational strategy: all (functional + tagging + literature)

resulting best candidates

rs2253206; rs2709376; rs11904814; rs6740584; rs17811997;rs13029936; rs1806584; rs2551941, rs2253206, rs7569963, rs7594560, rs4675690, rs889895, rs3732076, rs10559988, rs77713393