Neurobehavioral and neurodevelopmental profiles of a heuristic genetic model of differential schizophrenia- and addiction-relevant features: the RHA vs. RLA rats

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ABSTRACT

The Roman High- (RHA) and Low-(RLA) avoidance rat lines/strains were generated through bidirectional selective breeding for rapid (RHA) vs. extremely poor (RLA) two-way active avoidance acquisition. Compared with RLAs and other rat strains/stocks, RHAs are characterized by increased impulsivity, deficits in social behavior, novelty-induced hyper-locomotion, impaired attentional/cognitive abilities, vulnerability to psychostimulant sensitization and drug addiction. RHA rats also exhibit decreased function of the prefrontal cortex (PFC) and hippocampus, increased functional activity of the mesolimbic dopamine system and a dramatic deficit of central metabotropic glutamate-2 (mGlu2) receptors (due to a stop codon mutation at cysteine 407 in Grm2 -cys407*-), along with increased density of 5-HT2A receptors in the PFC, alterations of several synaptic markers and increased density of pyramidal "thin" (immature) dendrític spines in the PFC. These characteristics suggest an immature brain of RHA rats, and are reminiscent of schizophrenia features like hypofrontality and disruption of the excitation/inhibition cortical balance. RHA rats represent a promising heuristic model of neurodevelopmental schizophrenia-relevant features and comorbidity with drug addiction vulnerability.

Keywords: Roman high- and low-avoidance rats, neurodevelopmental genetic model, schizophrenia-relevant features, glutamate, GABA, mesocorticolimbic dopaminergic pathways, nucleus accumbens, medial prefrontal cortex, hippocampus

1. Introduction

Schizophrenia is a chronic mental disorder affecting about 1 % of the world population. The main manifestations of schizophrenia are classified into 'positive' symptoms (e.g. hallucinations, delusions, thought disorders), 'negative' symptoms (e.g. social withdrawal, apathy) and "cognitive" symptoms (e.g. attentional deficits, impairment of working memory). Antipsychotic medications are only partially effective: around 30% of patients are unresponsive to therapy (Sawa and Snyder, 2002; Powell and Miyakawa, 2006; Jones et al., 2011; Kapur, 2003; González-Maeso et al., 2008; Snyder, 2008).

Human genetic studies have revealed the existence of many susceptibility genes for schizophrenia (reviews by Sawa and Snyder, 2002; Powell and Miyakawa, 2006; González-Maeso and Sealfon, 2009; Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014; Flint and Munafo 2014). Interactions between susceptibility genes and environment are thought to play a prominent role (Powell and Miyakawa, 2006). Thus, the current view is that schizophrenia is a polygenic neurodevelopmental cognitive disorder that cannot be reduced to its psychotic symptoms and is not just a result of abnormal dopamine or serotonin functioning (Geyer et al., 2012; Millan et al., 2016; Sawa and Snyder, 2002; Powell and Miyakawa, 2006; Jones et al., 2011; Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014). There is an urgent need to establish newer and heuristic animal models that can take into account these insights from human studies and contribute both to our knowledge of the neurobiology of the disorder and to the development of new drugs/treatments capable of improving the negative symptoms and cognitive disfunctions of schizophrenia (Del Rio et al., 2014; Ellenbroek and Karl 2016; Fernando and Robbins 2011; Geyer et al., 2012; Jones et al., 2011; Powell and Miyakawa, 2006).

On the other hand, schizophrenia is associated with a remarkably high prevalence of cocaine, amphetamine, alcohol, cannabis, and nicotine use (reviewed by Giorgi et al., 2019). Experimental evidence accumulated in recent years supports the view that the pathologic substrate of schizophrenia may contribute to the susceptibility to addiction by facilitating the functional activity of the neural circuitry that mediates positive reinforcement (Chambers et al., 2001). Hence, the hypothesis implies that both the schizophrenia syndrome and vulnerability to addiction are primary disease symptoms, each directly caused by common neuropathological substrates, of which

mesocorticolimbic dopamine (DA) seems to be a crucial component (e.g. Chambers et al., 2001; Giorgi et al., 2019).

The main aim of the present article is to review, under a neurodevopmental focus, the most relevant neurobehavioral and molecular features of a rat model based on psychogenetic selection and breeding that presents divergent strain-dependent schizophrenia-relevant and addiction-related features/phenotypes: the Roman high- (RHA) and low-avoidance (RLA) rat lines/strains.

1. The Roman rats: main behavioral and psychopharmacological phenotypes

The Roman rat lines were established in Rome in the early 1960s through bidirectional selection and outbreeding of Wistar rats showing very high (RHA) vs. extremely low (RLA) rates of acquisition of the two-way active avoidance response (Bignami, 1965; Bignami and Bovet 1965). After the fifth generation of selection the two lines were moved to Birmingham, UK (Broadhurst and Bignami 1965), where selective breeding continued (e.g. Wilcock and Fulker 1973; Wilcock et al., 1981). Two outbred swiss sublines (named RHA/Verh and RLA/Verh), derived from the original lines from Birmingham, were established in Zurich, Switzerland in 1972 (Bättig and Schlatter, 1978; Bättig et al., 1976; Driscoll, 1976; Driscoll and Bättig, 1979; Driscoll and Käsermann, 1977; Driscoll et al., 1979, 1980; Duetsch and Bättig, 1977). Other outbred sublines, from the Zurich stock, were established in Cagliari, Italy (Giorgi et al., 1994, 1997, 2003a-b, 2005a-b, 2007; Sabariego et al., 2019), and Geneva, Switzerland (Steimer et al., 1997a,b). In addition, inbred Roman (RHA-I and RLA-I) strains, generated through brother/sister mating of the respective Swiss/Verh sublines, were established in Barcelona in 1995 (Driscoll et al., 1998, 2009; Escorihuela et al., 1997, 1999). Over 260 international articles have been published on the Roman rats (or using them as part of broader studies) during the fifty-five years since the original Roman rat lines were generated (150 of these have been published between 1995 and 2020).

Supplementary Table S1 summarizes the main findings and milestones achieved by the different laboratories that have conducted research in the past with the Roman rats as well as from those groups that continue to conduct and publish neurobiological research using the Roman rat lines/strains as subjects.

To sum up, compared with RHAs and various other rat strains/stocks, RLA rats display enhanced anxiety, fear and stress hormone responses in the face of unconditioned or conditioned threatening situations, as well as enhanced signs of frustration in reward devaluation tasks (reviewed in Giorgi et al., 2019; Papini et al., 2015; Steimer and Driscoll 2003; see Table S1 and references therein). Consistently, the anxious profile of RLA rats in different tests/tasks is attenuated or reversed by the administration of anxiolytic drugs and increased by known anxiogenic drugs (see a summary of these studies in Table S2).

On their side, compared with RLAs and other rat strains/stocks, RHA rats exhibit a large number of schizophrenia- and addiction-related traits, such as (see review by Giorgi et al., 2019):

(i)- enhanced novelty-induced locomotor activity (Table 1);

(ii)- increased impulsivity and novelty seeking (these are correlated traits that are related to both schizophrenia and addiction vulnerability in humans; Ahn et al., 2011; Brown et al., 2018; Ho et al., 2018,; Hoptman 2015; Magid et al., 2007; Roberti, 2004; Zuckerman 1996) (Table 1);

(iii) impaired attention, sensorimotor gating, startle habituation, working memory and cognitive flexibility (Table 1);

(iv) hyper-locomotion and enhanced stereotypies following acute administration of dopaminergic (DAergic) psychostimulants or morphine (Table 2);

(v) increased locomotor and DAergic accumbal sensitization to chronic amphetamine, cocaine, morphine and ethanol (Table 2);

(vi) enhanced operant lever pressing during acquisition, maintenance, extinction and reinstatement of cocaine self-administration, as well as enhanced preference for ethanol and natural rewards (Table 1);

(vii) increased functional tone of the mesolimbic DAergic system (Table 3).

As extensively reviewed in Giorgi et al. (2019), schizophrenia and vulnerability to drug addiction share some core features and/or mechanisms. In particular, for instance, the enhanced behavioral and neurochemical (e.g. DAergic) effects of acute and chronic

DAergic psychostimulants, and the increased functional tone of the mesolimbic DAergic system, are features that are considered to be at the core of both schizophrenia and addiction and are present in RHA rats relative to RLAs.

1.1. Psychopharmacological evidence: propsychotic and antipsychotic drug effects on locomotor activity, prepulse inhibition and social behavior preference in RHA vs. RLA rats

In this section we discuss mostly recent findings that have not been reviewed or discussed in our previous review (Giorgi et al., 2019).

The face, predictive and construct validity of RHA vs. RLA rats as a genetic model of schizophrenia-relevant and addiction-linked features are supported by the enhanced sensitivity of RHAs to the locomotor-stimulant and accumbal DA-releasing effects of acute and chronic psychostimulants, which indicate a higher functional tone of the mesolimbic/mesostriatal dopaminergic pathways of RHA vs. RLA rats (Table 2).

Moreover, in the context of the predictive validity of the RHA model, it is noteworthy that PPI of the acoustic startle is further impaired by the non selective DA D1/D2 receptor agonist apomorphine and improved by the DA D2/D3 receptor antagonist haloperidol in RHA, but not RLA rats (Oliveras et al., 2017). In addition, recent results from our laboratory reveal that oxytocin (which has antipsychotic effects in rodents and humans; Feifel and Reza 1999; Feifel et al., 2010, 2012, 2015; Lee et al., 2005) attenuates the PPI deficit of RHAs while being devoid of effects on RLA rats (Tapias-Espinosa et al., 2021; see Table 2). Also, RHA rats show less locomotor-reducing effects of haloperidol and are more sensitive to apomorphine-induced stereotypies (Gimenez-Llort et al., 2005; Oliveras et al., 2017) (Table 2). In the context of glutamatergic and serotoninergic transmission, which are involved in schizophrenia (e.g. Elert 2014; Elfving et al., 2019; González-Maeso et al., 2008, and references therein), clozapine (5-HT2A receptor antagonist) significantly attenuated the dizocilpine (NMDA receptor channel blocker)-induced PPI deficit only in RLA (but not RHA) rats, and the propsychotic drug 2,5-dimethoxy-4-iodoamphetamine (DOI, a HT2A receptor agonist) disrupted PPI in RLA rats in a dose-dependent manner (0.1, 0.25, 0.5 1.0 mg/kg) while only the 0.5 mg/kg dose impaired PPI in RHA rats (Oliveras et al., 2017). These attenuated effects of clozapine

and DOI in RHA rats seem to be consistent with the fact that there is an alteration of the 5HT2A/mGlu2 (metabotropic glutamate-2) receptor complex in these rats (as we will see in detail in the following sections; Gonzalez-Maeso et al., 2008; Wood et al., 2017). Finally, the locomotor-enhancing effects of the propsychotic drug dizocilpine are much more marked in RHA rats than in their RLA counterparts, and are more effectively attenuated by the atypical antipsychotics clozapine, ziprasidone and aripiprazole in RHA vs. RLA rats (Lavín, 2019; Oliveras et al., 2017; Torrecilla 2018; see Table 2).

Importantly, the face validity of RHA rats as a model of schizophrenia-related negative symptoms was evaluated in a series of social interaction tests. It was predicted that, compared with their RLA counterparts, RHAs would display less social preference and more profound social behavior impairments upon the administration of dizocilpine. Social preference was measured as the relative amount of social or non-social behavior shown by rats in a rectangular box with one hole in each of its distal sides (Sampedro-Viana et al., 2021). In this set-up, the rats are physically separated by placing them in two adjacent rectangular boxes. Each box has a hole at each end, the so called social and non-social hole, respectively; the social holes of each box are those facing each other. The rats are able to poke their noses through the social or non-social holes, thus giving an indication of respectively social or non-social investigative behavior (Gururajan et al., 2012; Panksepp et al., 1997; Sampedro-Viana et al., 2021). Social behavior preference is indicated in this test by the "social preference" index, that is, the percent of interaction time in the social hole relative to the sum of both holes. The predicted results were confirmed by the experiments; thus, drug-free RHAs displayed less social behavior preference than RLAs (Sampedro-Viana et al., 2021) while the social preference of RHA, but not RLA, rats was dramatically reduced by dizocilpine (to about 40% of vehicle-treated rats; Torrecilla 2018; Table 2). Remarkably, the impairment of social preference elicited by dizocilpine is attenuated, or even reversed, by the atypical antipsychotic drugs clozapine, aripiprazole and ziprasidone in RHA, but not RLA, rats (Lavín 2019; Table 2).

Collectively, the acute and chronic effects of psychostimulant drugs on locomotor activity and sensitization, the propsychotic effects of apomorphine and dizocilpine, the antipsychotic-like effects of haloperidol, clozapine, aripiprazole, ziprasidone, and oxytocin, and their pharmacological effects on PPI and/or social behavior, give experimental support to the predictive and face validity of RHA rats as a model of schizophrenia-relevant features (Table 2). Furthermore, the foregoing results highlight

the involvement of glutamatergic, serotoninergic and mesolimbic dopaminergic mechanisms in the phenotypic traits of RHA rats, which provides support to the construct validity of the RHA model. These contentions are further supported by the cognitive and attentional deficits of RHAs, relative to RLAs and other rat strains/stocks used as external controls (Table 1).

1.2. Developmental onset of behavioral phenotypes in the RHA model

Notably, some of the schizophrenia–related behavioral phenotypes of the RHA model follow a developmental pattern. Thus, compared with RLAs (and with outbred rats, in some cases), male RHA rats display slight PPI deficits at puberty (postnatal days –PND-50-56), and such an impairment is much more marked in adulthood (≥PND100), but is not present at prepuberty (PND30) (del Río et al., 2014; Oliveras et al., 2015; Soria-Ruiz 2021). On the other hand, the PPI impairment in female RHA rats clearly emerges at puberty (PND50-56) and continues during adulthood (≥ PND100), but is not observed at pre-pubertal age (Río-Álamos et al., 2019; Soria-Ruiz 2021). Likewise, our ongoing studies show that the deficit of habituation of the acoustic startle response in RHA rats emerges in adulthood.

A very consistent finding is the marked hyperactivity that RHA rats of both sexes exhibit in open field-like tests and in tunnel labyrinths (involving no explicit reward), which is already present at early pubertal ages (around PND30-35; e.g. Escorihuela et al., 1997; Fernández-Teruel et al., 1991a, 1992b, 2002c) and persists through adolescence and adulthood (e.g. Castanon and Mormède 1994; Escorihuela et al., 1999; Estanislau et al., 2013; Lopez-Aumatell et al., 2009b; Steimer and Driscoll 2003). Conversely, when exposed to test situations involving more explicit and hippocampus-dependent approach-avoidance conflict, such as the elevated plus-maze or the dark/light (two-compartment) box tests, which involve clear "safe" vs. threatening spaces (Bannerman et al., 2004, 2014; Gray and McNaughton 2000), the hyperactivity of RHA rats (i.e. increase of horizontal activity or crossings between the "safe" and threatening spaces) is not observed at prepubertal or pubertal ages (PND28-35 or PND56, respectively), and only appears consistently at young adulthood (Escorihuela et al., 1999; Fernández-Teruel et al., 2002c; Steimer and Driscoll 2003).

Some of the stress-related behavioral/endocrine phenotypes of RHA rats also follow a developmental onset, i.e. they emerge in young adulthood, after PND 90-100, as in the case of the stress-induced ACTH response (Castanon and Mormède 1994; Castanon et al., 1994). Also in this context, relative to RLA and genetically heterogeneous rats (i.e. the "National Institutes of Health heterogeneous stock rat", or, HS rats), RHA rats show a marked deficit in novelty/stress-induced grooming behavior at pubertal age and young adulthood (PND 56-70) that is not present at prebubertal ages (PND 28-35; Estanislau et al., 2013; Steimer and Driscoll 2003). It seems relevant here to underscore the similarity between the decreased grooming behavior and, to a certain extent, hyperactivity, of RHA rats and that observed in the neonatal ventral hippocampus lesion (NVHL) rat model of schizophrenia. The NVHL model is probably the most used neurodevelopmental model of schizophrenia, and is considered to have good face, construct and predictive validity for the different symptoms of the disorder as well as regarding the associated neurobiological mechanisms or processes (e.g. Tseng et al., 2009). Interestingly, much like RHA rats, NVHL rats also show a deficit in grooming behavior at young adulthood, but not at prepubertal age, that depends on the integrity of the PFC (Estanislau et al., 2013; Flores et al., 2005; Tseng et al., 2009).

Regarding the negative symptom spectrum of schizophrenia, we have recently found that the deficit of social interaction preference that characterizes adult male and female RHA rats (vs. RLA and outbred HS rats) is not present in adolescent animals at PND50 (Sampedro-Viana et al., 2021; Soria-Ruiz 2021; Table 1). Thus, adolescent male RHA rats exhibit a social interaction preference of 71%, which is not different from a 77% social preference of adolescent RLA rats (Soria-Ruiz 2021). Interestingly, during adulthood these percentages evolve up to approximately 50% in RHA (i.e. they do not show preference for the "social" hole of the testing cage) and 60-70% in RLA rats, showing significant differences between both strains (Sampedro-Viana et al., 2021). Of note, no differences in social preference between female RHA and RLA rats of either age have been found (Soria-Ruiz 2021). Thus, there is an age- and sex-linked pattern of appearance of the social interaction deficit in RHA rats, which opens a new research path on the developmental onset and gender-dependent neurobiological processes related to some schizophrenia-linked symptoms in this rat strain.

It is also noteworthy that environmental conditions during postnatal development may enduringly influence some of these genetically-based phenotypic profiles. Thus, neonatal

handling (NH)-stimulation (administered from PND1 to PND21) produces very long-lasting improvements of PPI and cognitive performance in RHA rats, along with strain-dependent volume alterations of HC and AMY (Rio-Álamos et al., 2017b, 2019), and it also increases social interaction preference more markedly in RHAs than in RLA rats (Sampedro-Viana et al., 2021). On the other hand, social isolation rearing (SIR) in rats is considered a model of early adversity-induced schizophrenia-like symptoms/features with face and predictive validity (see reviews by Jones et al., 2011; Fone and Porkess 2008). SIR produces profound deleterious and enduring effects in RHA rats (but not in RLA rats), as shown by marked increases in anxiety, enhanced hyperactivity, and impairments of PPI and spatial cognition (Oliveras et al., 2016; Sánchez-Gonzalez et al., 2019). These findings demonstrate that environmental influences on neurodevelopmental processes may affect the development of several of the above-mentioned genetically-based schizophrenia-relevant phenotypes, while also showing an increased sensitivity of RHA (vs. RLA) rats to the effects of particular developmental interventions on those phenotypes.

Although further developmentally-oriented studies are warranted, the above reviewed findings suggest an altered neurobehavioral development in RHA rats which may be consistent with their schizophrenia-related phenotypic profiles. This will be reviewed and discussed more in depth in the following sections.

2. Brain features of RHA vs RLA rats: a neurodevelopmental perspective

3.1 The mesocorticolimbic DA system: Recent developments related to the schizophrenia- and drug addiction-relevant profile of the RHA model

In this and the following sections we present and discuss mostly recent findings with the RHA model (vs RLA rats and other strains or models) that have neurodevelopmental implications for the model and have not been included or discussed in our previous reviews (Giorgi et al., 2019; Driscoll et al., 2009).

A recent report has shown that, besides exhibiting increased cocaine self-administration and resistance to extinction (as previously shown by Fattore et al., 2009), compared with RLA rats RHAs display higher propensity to cocaine-induced relapse, a trait that may be due to the larger DA release in the NAcc of RHA rats in response to cocaine rather than

to postsynaptic DA receptors-mediated mechanisms (Dimiziani et al., 2019). That study also demonstrated that when cocaine-induced relapse occurs, it is mainly mediated by postsynaptic D2 rather than D3 receptors. Accordingly, cocaine-induced relapse is inhibited in both Roman rat lines by pretreatment with the D2 receptor antagonist, L741,626, but not with the D3 receptor antagonist, SB-277,011A (Dimiziani et al., 2019). However, there is consistent evidence that pretreatment with D3 receptor antagonists reduces reinstatement of cocaine-seeking behavior in other rat strains (Vorel et al., 2002) and in squirrel monkeys (Achat-Mendes et al., 2010), which, therefore, highlights the importance of the differences between strains and species. Another recent and potentially important finding from the same group was that, compared with RLA rats, RHAs exhibit lower striatal D2/D3 receptor adaptations (i.e. lesser functional supersensitivity) following chronic D9-tetrahydrocannabinol (THC) administration (Tournier et al., 2018). Together with the increased striatal mRNA expression of CB1 (cannabiboid type 1) receptor in RHA rats, these findings may suggest that differences between both rat lines in the balance of CB1-D2/D3 transmission could be related to the divergent responses to abused drugs of RHA and RLA rats (Tournier et al., 2018). Of note, the endocannabinoid systems, acting through several signaling pathways, seem to be involved in the regulation of neural cell survival, neurogenesis and neuronal maturation across development (e.g. Paraíso-Luna et al., 2020; Sagredo et al., 2018). Hence, these divergent THC effects and CB1 expression in RHA vs. RLA rats may suggest that differences in the endocannabinoid systems might have a role on the particular neurobehavioral developmental profiles of the former strain. This possibility deserves further research.

On the other hand, in a replication and extension of Tournier et al. (2013) study, Bellés et al. (2021) have reported that impulsivity and novelty seeking (novelty preference) traits are positively related in the Roman rats (Bellés et al., 2021). Both phenotypes are negatively related with D2/3 autoreceptor availability in ventral striatum and dorsal striatum, which is decreased in in the high-impulsive/ novelty-preferring RHA animals (Bellés et al., 2021). A novel finding of this study is, however, the existence of some differences between RHA and RLA rats regarding amphetamine (AMPH)-induced DA release in relation to their novelty preference and impulsivity profiles. This suggests that *"...Impulsivity and novelty preference are related but mediated by overlapping, yet dissociable, DA-dependent mechanisms in striatum that may interact to promote the emergence of an addiction-prone phenotype"* (Bellés et al., 2021). As mentioned earlier,

locomotor and DAergic sensitization are considered to play a key role in several aspects of addiction. In particular, resistance to extinction of cocaine-seeking behavior, as shown by RHA rats, is thought to reflect an altered glutamatergic and/or dopaminergic activity in the prefrontal cortex (Millan et al., 2011; Marchant et al, 2012; Peters et al, 2008) and mesolimbic (Self et al., 2004) pathways, which in turn are linked to an inability to inhibit inappropriate (impulsive) responding to drug-associated stimuli (Jentsch and Taylor, 1999; Kalivas et al., 2005). Of note in this context, prefrontal cortex dysfunctions are associated with impulsivity (Crews and Boettiger, 2009; Dalley et al., 2002), thus suggesting a common mechanism that could affect impulsive behavior and persistence of cocaine-seeking behavior in RHA rats. Accordingly, cocaine-sensitized RHA rats (but not RLA rats) show a marked reduction of DAergic transmission in the mPFC (Giorgi et al., in preparation).

The functional tone of central DAergic systems is though to be related to the intensity of locomotor behavior (e.g. Flores et al., 2005; Giménez-Llort et al., 2005, and references therein). Accordingly, from a developmental perspective, the marked and consistent behavioural disinhibition and hyperactivity observed across different novelty conditions in prepubertal and pubertal RHA rats (as mentioned in section 2.2), suggest that central DA systems may be altered during early development in these animals. Although this hypothesis has yet to be examined, it is indirectly supported by the altered expression of neurodevelopment-related pre- and post-synaptic markers found in the PFC of RHA rats (as we will discuss in the following sections; Elfving et al., 2019). Since DA systems interact with GABA and glutamate systems in the PFC, it seems conceivable that developmental abnormalities of mesocorticolimbic DA function may be associated to altered interactions with, and maturation of prefrontal (and probably other) GABA and glutamate systems, which are considered of crucial importance for the function of the PFC and for the balance between excitation and inhibition (e.g. Tseng et al., 2009). This would also be consistent with the reduced activity and volume of the mPFC found in adult RHA rats (Meyza et al., 2009; Rio-Álamos et al., 2019; Tapias-Espinosa et al., 2019; Table 3), as well as with both their enhanced behavioral and neurochemical sensitivity to the effects of acute and chronic DAergic psychostimulants and their vulnerability to addiction (reviewed by Giorgi et al., 2019),

3.2 Glutamate-serotonin interactions in the PFC

Considerable experimental evidence supports the view that serotonin transmission is crucially involved in impulsivity. The general consensus is that an increase in central serotonergic function is associated with a decrease in impulsivity and impulsive sensation seeking (Dalley and Robbins, 2017; Soubrié, 1986; Zuckerman, 1996). In this sense, activation of 5-HT_{2A} receptors seems to facilitate some forms of impulsive behavior, whereas antagonism of these receptors produces reductions of several types of impulsive responses in rodents and humans (reviewed by Dalley and Robbins, 2017, and Klein et al., 2014). Accordingly, the density of 5-HT_{2A} receptors (a site of action of atypical antipsychotic drugs) is higher in the PFC of RHA than RLA rats, and there is a positive correlation between 5-HT_{2A} receptor density and premature/impulsive responses in the 5-CSRT task in the RHA strain (Klein et al., 2014).

The differences in 5-HT_{2A} receptor density between RHA and RLA rats appear to be linked to functional differences in glutamate transmission. Thus, it has recently been shown that, due to a stop codon mutation at cysteine 407 in *Grm2* (cys407* mutation), the gene encoding the metabotropic glutamate-2 receptor (mGlu2) (Wood et al., 2017; see also Fomsgaard et al., 2018), RHA, but not RLA, rats display a severe disruption of the heteromeric 5-HT_{2A}/mGlu2 receptor complex (Fomsgaard et al., 2018; Klein et al. 2014; see González-Maeso et al., 2008) (Table 3). Hence, there is a dramatic reduction in the density of mGlu2 receptors in the cerebral cortex, hippocampus (HC) and striatum (STR), associated with an increase of 5-HT_{2A} receptor density in the frontal cortex of RHA rats (Elfving et al., 2019; Fomsgaard et al., 2018; Klein et al. 2014). Of note in this context, chromatin immunoprecipitation assays have revealed an increased trimethylation of histone 3 (H3) at lysine 27 (H3K27me3) at the promoter region of the gene encoding the 5-HT_{2A} receptor in the STR of RHA rats (Fomsgaard et al., 2018). Such an increment in H3 trimethylation may be the cause of the above-mentioned increase of 5-HT_{2A} receptor density (see Fomsgaard et al., 2018). Interestingly, this molecular profile is reminiscent of the alterations found in the cortex of drug-free schizophrenic patients and, accordingly, it has been shown that the heteromeric 5-HT_{2A}/mGlu2 receptor complex is critically involved in the pharmacologic effects of atypical antipsychotics (Fribourg et al., 2011; Gonzalez-Maeso et al. 2008; Moreno et al., 2012, 2016; Muguruza et al., 2013). Also consistent with the above findings, the expression of the gene encoding the mGlu2 receptor is significantly decreased in both PFC and STR of RHA rats (Fomsgaard et al.,

2018). As regards the Akt/GSK3 signaling pathway, which is a downstream point of convergence of the serotonin and glutamate transmission, it has been found that the phosphorylation levels of GSK3β at tyrosine 216 and β-catenin levels are higher in the PFC of RHA than RLA rats (Fomsgaard et al., 2018). These results point to a region-specific regulation of the 5-HT_{2A} receptor in RHA rats that is probably due to the absence of mGlu2 receptors (Wood et al., 2017), and that may result in a strain-dependent differential regulation of downstream signaling pathways (Fomsgaard et al., 2018). It is also remarkable that the levels of the NMDA2B subunit of the NMDA receptor, as well as the expression of *Grin2b* mRNA (NMDA2B), are higher in the HC and PFC of RHA vs. RLA rats (Elfving et al., 2019; Table 3), since both strain-dependent differences may determine distinct downstream regulation patterns of neural activity. Therefore, the alterations observed in the 5-HT_{2A}/mGlu2 complex and NMDA receptors in RHA rats may at least partly account for some of the schizophrenia-related traits observed in this strain, such as the enhanced responsivity to the locomotor-stimulating effects of dizocilpine, the dizocilpine-induced impairment of social behavior, and the differential effect of clozapine on both dizocilpine-impaired PPI performance and dizocilpine-stimulated locomotor activity in RHA vs. RLA rats (Lavín 2019; Oliveras et al., 2017; Table 2).

Mounting evidence suggests that glutamate-mediated synaptic plasticity, in particular long-term depression (LTD), plays an important role in synaptic pruning in the PFC during adolescence. Because the disruption of synaptic plasticity may derail the normal maturation of executive function (Selemon, 2013), it is likely that the absence of the mGlu2 receptor in the RHA strain may cause synaptic alterations, thereby hindering the development and maturation of the brain (Elfving et al., 2019). Although the mechanisms underlying these alterations remain largely unknown, recent studies have revealed a functional interaction between the mGlu2 receptor and BDNF in vitro in which the activation of the mGlu2 receptor by a selective agonist enhances BDNF-induced *BDNF* gene expression, whereas BDNF down-regulates the expression of the *mGluR II* gene (Suzuki et al., 2017).

3.3. Synaptic alterations and neurotrophic factors in the PFC

Dysregulation of neurotrophic factors like BDNF has long been associated with the cellular, cytoarchitectural and volumetric alterations seen in schizophrenia (Angelucci et al., 2005). Post-mortem studies in the brain of schizophrenia patients have shown significant alterations in BDNF mRNA and protein levels in the cerebral cortex and HC (Durany et al., 2001; Reinhart et al., 2015; Takahashi et al., 2000). In humans, the Val(66)Met single-nucleotide polymorphism in the *BDNF* gene is associated with increased schizophrenia risk (Lencz et al., 2009; Ursini et al., 2016). Furthermore, when this mutated human gene is introduced in an animal model, the resulting genotype is associated with deficits in sensorimotor gating processes (Notaras et al., 2017). Accordingly, compared to RLA rats, the protein levels of BDNF are lower in the PFC and higher in the HC of RHA rats (Elfving et al., 2019; Serra et al., 2018), and the levels of the Polysialilated-Neural Cell Adhesion Molecule (PSA-NCAM), which interacts with BDNF and its receptor facilitating BDNF signaling (Serra et al., 2018; Bonfanti, 2006), are generally higher in the dorsal HC of RHAs relative to RLAs (Serra et al., 2018). These changes in neurotrophic factors seem to be compatible with the aforementioned alterations in activity and volume of the PFC and HC, and the enlargement of lateral ventricles, in RHA rats (Meyza et al., 2009; Rio-Alamos et al., 2017b, 2019; Tapias-Espinosa et al., 2019; Table 3).

BDNF plays a key role in synaptic plasticity and communication during neurodevelopment (Favalli et al., 2012; Kowianski et al., 2018; Nieto et al., 2013) and synaptic alterations have been reported in the brain of schizophrenia patients (Focking et al., 2015). Accordingly, RHA rats also show altered levels of synaptic components, including the postsynaptic density (PSD) proteins Homer1 in PFC (Elfving et al., 2019; Table 3) and Homer3 in whole brain (Sabariego et al., 2011). Abnormalities in the PSD are linked to neurodevelopmental diseases such as autism spectrum disorder and schizophrenia (Kaizuka and Takumi, 2018). The PSD protein Homer1 mediates the glutamatergic, serotonergic and dopaminergic receptor signaling at the postsynaptic site (de Bartolomeis et al., 2013a,b; Iasevoli et al., 2011), and Homer1 polymorphisms are associated with differential responses to treatment in schizophrenia (Spellmann et al., 2011). In line with the increased expression of Homer1 in RHA rats, differential effects of antipsychotic and propsychotic drugs targeting dopamine, glutamate and serotonin

receptors have been found in RHA vs. RLA rats (Oliveras et al., 2017; Lavín 2019; Torrecilla 2018; see Table 2).

RHA rats also display increased expression and protein levels of Nrg1 (neuregulin-1) in the PFC (Elfving et al., 2019; Table 3). Nrg1 has a role in regulating the excitatory/inhibitory neurotransmission at the PSD and is linked to schizophrenia risk (Mostaid et al., 2016). In fact, Nrg1 modulates sensorimotor gating, and disruption of Nrg1 signaling impairs hippocampal-prefrontal synchrony and topdown attention, as seen in animal (Rhein et al., 2013; Karl et al., 2011; Tan et al., 2018) and human studies (Roussos et al., 2011; Hong et al., 2008); thus, an increased *NRG1* expression is positively associated with schizophrenia-like pathology and PPI impairment (Deakin et al., 2009; Karl et al., 2011; Rhein et al., 2013; Swerdlow et al., 2012).

Moreover, upregulation in presynaptic SNARE components is observed in the brain of schizophrenia patients (Ramos-Miguel et al., 2015): the levels of two of the core proteins in the SNARE complex, SNAP25 and VAMP (Cupertino et al., 2016), are altered in the PFC and HC of RHA rats (Table 3). Thus, SNAP 25 expression is upregulated in the PFC of the RHA strain (Elfving et al., 2019). SNAP25 controls exo/endocytic processes at the presynaptic terminal and plays an important role in regulating postsynaptic receptor trafficking and synaptic plasticity (Antonucci et al., 2016). Overexpression of SNAP 25 leads to memory deficits (McKee et al., 2010), as also shown for the RHA strain (Oliveras et al., 2015; Rio-Álamos et al., 2019). In the HC, *VAMP1* and *SNAPIN* gene expression and protein levels are decreased in RHA rats (Elfving et al., 2019). VAMP proteins are essential for the fast synaptic-vesicle exocytosis and recycling and for the insertion of glutamate receptors into the postsynaptic plasma membrane (Deak et al., 2004; Hussain and Davanger, 2015; Gu and Huganir, 2016), whereas SNAPIN seems to be an important component of the SNARE-mediated neurotransmitter release (Ilardi et al., 1999). The alterations in NMDA receptor subunits observed in RHA rats could be linked to the observed variations in the SNARE complex, as this complex regulates NMDA receptor trafficking (Gu and Huganir, 2016) and mediates the insertion NMDA2B subunits at postsynaptic sites (Hussain et al., 2016). Thus, it is conceivable that the increased sensitivity to dizocilpine-induced hyperactivity and dizocilpine-impairment of social behavior in RHA rats are related to alterations in the SNARE complex (Lavín 2019; Oliveras et al., 2017; Torrecilla 2018; see Table 2).

3.4 Pyramidal dendritic spines in the PFC

Abnormal neurodevelopment and an immature state of the PFC have been described in the brains of schizophrenia patients (Hagihara et al., 2014). There is consensus that impaired PFC function and connectivity is one of the main features of schizophrenia and is associated with the cognitive deficits that characterize this disorder (Chari et al., 2019; Ferrarelli et al., 2015; Pu et al., 2019).

Many genes examined in the RHA and RLA strains by Elfving et al. (2019) are dynamically expressed in the PFC during lifetime, as evidenced from the human Brain Cloud dataset (Colantuoni et al., 2011; Elfving et al., 2019). These genes are up- or downregulated during the time windows of neurodevelopment in which executive function is established (Elfving et al., 2019; Silbereis et al., 2016; Taylor et al., 2015) and, consequently, they may have an important role in the establishment of some of the cognitive processes that are disrupted in the RHA strain. Although the animals used in the study by Elfving et al. were adult RHA (and RLA) rats, the synaptic markers Homer1, Nrg1, Syp, BDNF, Grin2B and Drd1 were upregulated in the PFC with a pattern that resembled that observed in human children or adolescents (Elfving et al., 2019). Further studies aimed at assessing the expression of these synaptic markers throughout the lifespan are warranted to confirm that the upregulation pattern of those genes in the PFC of RHA rats is indeed the expression of an "immature" phenotype.

There is strong evidence that GSK3β and β-catenin are involved in spine stability and synaptic plasticity both during development and in adulthood (Maguschak and Ressler 2012; Mills et al., 2014; Ochs et al., 2015). Thus, the increased phosphorylation levels of GSK3β at tyrosine 216 and increased β-catenin levels in the PFC of RHA rats (Fomsgaard et al., 2018) could be of great importance for understanding the neurobiological substrates of the schizophrenia-like neurobehavioral phenotype of the RHA model. This possibility prompted the study of differences in spine density of pyramidal neurons in the PFC of the RHA vs RLA rats. It was found that, compared with their RLA counterparts, RHA rats exhibit a higher number of dendritic spines, due to an increased density of "thin" spines, but, on the other hand, they show a lower percentage of large and "mature" (i.e., mushroom and stubby) spines relative to the "total" number of spines of any type (Sánchez-González, 2018; Sánchez-González et al., 2021; Table 3). Of note, two

important regulators of dendritic spine morphogenesis are the scaffolding protein Homer 1 (Sala et al., 2001) and the neurotrophin BDNF (Tyler and Pozzo-Miller 2003), which are upregulated in the PFC of RHA rats (Elfving et al., 2019).

Animal studies show that the density of spines is significantly higher during early adulthood and then progressively declines via pruning during adulthood (Arnsten 2011; Holtmaat et al., 2005; Silva-Gomez et al., 2003; Tjia et al., 2017). Also, thin spines predominate in the human adolescent brain (Holtmaat et al., 2005). Dendritic spines are dynamic structures (Kasai et al., 2010), and their morphology changes during development, with thin spines transitioning to mushroom spines, which are more stable in shape and density (Bourne and Harris 2007; Glausier and Lewis 2013). Therefore, spine density and morphology can reflect neuronal development, plasticity and connectivity (Glausier and Lewis 2013; Kasai et al., 2003; Silva-Gomez et al., 2003). An over-representation of small, more unstable spines and/or a decreased proportion of large, more stable spines in the PFC is likely causing the impaired cognitive functions seen (Kasai et al., 2003, 2010). Dendritic spine alterations in cortical pyramidal neurons have consistently been reported in postmortem studies of humans with schizophrenia and appear to be related to the cognitive symptoms of the disorder (Black et al., 2004; Glantz and Lewis 2000; Hill et al., 2006; Moyer et al., 2015). Altogether, these observations support the notion of an immature developmental state of the PFC in RHA rats that could contribute to a PFC dysfunction and may be involved in the schizophrenia-like behavioral alterations characterizing this strain.

Small thin spines are described as “learning” spines, since they are transient and are involved in rapid plasticity, and they seem to correspond to “silent synapses”, expressing NMDA but not AMPA receptors (Glausier and Lewis 2013; Kasai et al., 2003, 2010). In contrast, large spines, represented by the stubby and mushroom types, are considered “memory” spines, which are more stable than the small ones and are involved in long-term synaptic plasticity, associated with AMPA receptors (Glausier and Lewis 2013; Kasai et al., 2003). This is very consistent with the findings of increased expression levels of the NMDA receptor subunit GluN2B in the PFC of the RHA rats, while there is no difference in AMPA receptor subunits (Elfving et al., 2019). The NMDA receptor with GluN2B subunits is associated with spine density regulation (Liu et al., 2017) and with “silent synapses” (Han and Heinemann 2013; Polli and Kohlmeier 2019). Moreover,

there is a genetic association between this receptor subunit and schizophrenia (Martucci et al., 2006).

In addition, glial cells play an essential role in synaptic regulation (Bernstein et al., 2009). The major type of glia cells, astrocytes, are main components of the "tripartite synapse" (Papouin et al., 2017; Santello et al., 2019), and as such are involved in synaptic function, plasticity and maturation. Changes in astrocyte number in the PFC have been linked to several mental disorders, including schizophrenia (Lima et al., 2014; Schnieder and Dwork 2011). Microglia are also involved in synaptic maturation (Mallya et al., 2019). No difference in microglia numbers in the PFC of RHA and RLA rats has been found, whereas a marked difference in astrocytes (RHA > RLA) has been observed (Sánchez-González, 2018; Sánchez-González et al., 2021; Table 3). Microglia's role during adolescence is related to synaptic pruning and synaptic elimination (Mallya et al., 2019) and, since RHA rats show a higher rather than reduced number of dendritic spines, one would not expect an increased number of microglia. Conversely, it seems very likely that, given the important role of astrocytes in the development of cortical neural circuits (Macht 2016) and in the stabilization (Bernardinelli et al., 2014) and maturation of excitatory synapses (Reemst et al., 2016), the increased number of astrocytes observed in the PFC of the RHA rats is associated with the dendritic spine alterations in this strain. Thus, the increase in astrocytes may be a compensatory mechanism to help stabilize a larger number of thin spines in the PFC of the RHA strain. Astroglia release D-serine, a co-agonist of the NMDA receptor (Meunier et al., 2017), which could lead to overstimulation of NMDA receptors containing the GluN2B subunit. On the other hand, glutamate regulation is essential for the maturation of synaptic dendrites (Mattison et al., 2014) and astrocytes regulate glutamate release through activation of their mGlu2/3 receptors (Tang and Kalivas 2003). The stop codon in the DNA of RHA rats that results in the absence of mGlu2 receptors (Fomsgaard et al., 2018; Wood et al., 2017) may lead to malfunction of astroglia in this strain, which may sustain their immature synaptic phenotype. Indeed, dysfunction of astroglia during brain development can contribute to neurodevelopmental disorders (Reemst et al., 2016). The fact that astroglia (but not microglia) is altered in RHA rats supports this idea (Sanchez-Gonzalez, 2018; Sanchez-Gonzalez et al., 2021).

3.5 Excitatory/inhibitory balance in the PFC

Excitatory pyramidal cells receive inhibitory input from PV interneurons, a subtype of GABAergic interneurons (Gonzalez-Burgos et al., 2015), and interneuron dysfunction is believed to be one of the causes behind the neurocircuitry disruption linked to schizophrenia (Marin 2012). No differences between RHA and RLA rats were observed in numbers of PV-containing GABAergic interneurons in the mPFC (Sanchez-Gonzalez et al., 2021). This is in accordance with lower PV mRNA expression and density of PV-immunoreactive puncta rather than a reduced number of PV interneurons, as found in the brain of schizophrenia patients (Beasley et al., 2002; Chung et al., 2016; Enwright et al., 2016; Glausier et al., 2014; Lewis et al., 2012). About half of the genes representing the transcriptomic immaturity of the PFC of schizophrenia patients are related to the development of PV-interneurons and astroglia (Hagihara et al., 2014). One of these GABAergic interneuron-specific genes expressed by PV interneurons is *ErbB4* -the receptor for the trophic factor neuregulin 1, Nrg1-, which is important for spine formation in cortical pyramidal neurons (Agarwal et al., 2014; Yin et al., 2013). Nrg1 increases spine density but it is through ErbB4 that it regulates spine growth (Cahill et al., 2013), and impaired Nrg1/ErbB4 signaling leads to dendritic spine destabilization and glutamatergic hypofunction (Li et al., 2007a). Interestingly, the RHA rats present increased expression levels of Nrg1 in the PFC (Elfving et al., 2019), which could explain the increased spine density observed in this strain. ErbB4 signaling is required for attention (Tan et al., 2018) and, since attentional deficits (linked to impulsivity) are one of the main behavioral features of RHA rats (e.g. Esnal et al., 2016; Klein et al., 2014; Oliveras et al., 2015; Río-Álamos et al., 2019; Tapias-Espinosa et al., 2019), it may be hypothesized that Nrg1/ErbB4 signaling is impaired in this strain. It is therefore warranted to assess whether RHA rats show PV neuron specific ErbB4 dysfunction across development.

GABAergic interneurons in the PFC are innervated by dopaminergic fibers originating in the ventral tegmental area (VTA) and express D1 and D2 receptors, which facilitate local GABAergic function in the PFC. Of note, D1 receptors are involved in NMDA receptor trafficking to postsynaptic membranes (see Tseng et al., 2009, and references therein). In the PFC, RHA rats show an increased density of D1 and NMDA2B receptors (Elfving et al., 2019) but, as previously mentioned, they do not differ from RLA rats regarding the number of PV-containing GABA interneurons. However, we have recently found that

PV+ labeling is decreased by about 60 % in RHA rats in PFC neurons activated (as measured by c-fos expression) following a PPI session (Table 3). This finding suggests that, when activated by an attention-related task (i.e. PPI), the PFC of RHA rats exhibits a relatively low or disrupted inhibitory activity due to a decreased activation of PV GABAergic neurons (Tapias-Espinosa 2020; Table 3).

In view of the above mentioned findings, together with the altered densities of D1, 5-HT_{2A}, NMDA and mGlu2 receptors and the upregulation of the synaptic markers Homer1, BDNF, SNAP25 and Nrg1, it is conceivable that the PFC of RHA rats shows a developmental dysregulation of excitation/inhibition balance. This would cohere with the aforementioned volumetric and functional (c-fos) frontocortical and HC differences observed between RHA and RLA rats (García Falgueras et al., 2012; Meyza et al., 2009; Rio-Alamos et al., 2019; Tapias-Espinosa et al., 2019; Table 3). Such developmental alteration may be due to dysfunctional dopamine/GABA/glutamate interactions, and may lead to a decreased cortical function accounting, at least in part, for the schizophrenia-relevant and drug addiction-related phenotypic profile of the RHA strain (see Figure 1 and Figure 2).

3. A neurodevelopmental glutamatergic hypothesis

As we have seen in the previous sections several behavioral and endocrine phenotypes of the RHA model emerge in the early postpubertal period or during young adulthood, and such a developmental onset may be reminiscent of some schizophrenia-linked features. The altered regulation in the expression of particular receptors, neurotrophic factors and synaptic markers in the PFC and HC of RHA rats (e.g. Homer1, Nrg1, Syp, Bdnf, Grin2B, Snap25, Drd1, Snapin,Vamp1), collectively resemble an immature/adolescent stage of brain development in these rats, in keeping with the neurodevelopmental hypothesis of schizophrenia. Several of these marker alterations have been related with attentional/cognitive phenotypes and with schizophrenia, and the extended variations observed are in agreement with the notion that alterations of synaptic networks are one of the main pathophysiological underpinnings of schizophrenia (Elfving et al., 2019, and references therein).

Due to the cys407* mutation in *Grm2*, the mGlu2 receptor is missing in RHA rats during development and throughout their lifetime, which probably leads to adaptations in 5-HT_{2A} receptors, serotonergic transmission, and in other systems, such as the mesocorticolimbic dopaminergic pathways. It is noteworthy that mGlu2 Receptor Knockout (*mGlu2-KO*) mice exhibit a variety of phenotypes indicating enhanced vulnerability to drug addiction and schizophrenia-relevant features (Morishima et al., 2005), including: (1) increased susceptibility to develop locomotor sensitization and conditioned place preference upon repeated cocaine administration, (2) augmented extracellular levels of dopamine and glutamate in the NAcc following acute cocaine administration, (3) hyperactivity under novelty/stressful conditions, (4) augmented hyperactivity following acute amphetamine, (5) impaired spatial working memory (De Filippis et al., 2015; Hideshima et al., 2018; Morishima et al., 2005), (6) some signs of decreased anxiety in an open-field-like test and an active coping style (De Filippis et al., 2015; Hideshima et al., 2018; Morishima et al., 2005). These phenotypes of *mGlu2-KO* mice closely resemble the psychostimulant-induced sensitization of locomotor activity, increased mesolimbic dopamine and glutamate function following chronic treatment with psychostimulants, hyperactivity, active coping style and cognitive phenotypic profiles observed in the RHA model (Giorgi et al., 2019; Piras et al., 2010, 2014; Serra et al., 2018). Moreover, also regarding the parallelism between *mGlu2-KO* mice and RHA rats, it is remarkable that the former exhibit a reduced responsivity to the behavioral effects of psychotomimetic 5-HT_{2A} receptor agonists like 2,5-dimethoxy-4-iodoamphetamine (DOI) or lysergic acid diethylamide (LSD) and the 5-HT_{2A} receptor antagonist, clozapine. This is consistent with the fact that the 5-HT2A/mGlu2 receptor complex is disrupted (Hideshima et al., 2018; Moreno et al., 2011), whereas the density of 5-HT_{2A} receptors in the PFC, as determined with the radiolabeled ligand [3H]ketanserin, is preserved (Hideshima et al., 2018; Moreno et al., 2011). Likewise, relative to RLA rats, the DOI-induced PPI impairment and the clozapine antagonism of the dizocilpine-induced PPI impairment (Oliveras et al., 2017) are reduced in RHA rats, although [3H]ketanserin binding in the PFC is also preserved (Fomsgaard et al., 2018; Klein et al., 2014). Hence, it appears that at least some of the adaptive changes due to the permanent absence of mGlu2 receptors in RHA rats closely resemble those seen in the *mGlu2-KO* mice. Importantly, the reduced effects of the 5-HT_{2A} receptor agonists, DOI and LSD, and the 5-HT_{2A} receptor antagonist, clozapine, in both *mGlu2-KO* mice and RHA rats, are consistent with the hypothesis that both receptors of the 5-HT_{2A}/mGlu2 complex in the PFC interact to

mediate some antipsychotic and propsychotic drug effects, thus perhaps being involved in some schizophrenia-relevant manifestations (Fribourg et al., 2011; González-Maeso et al., 2008).

Considerable evidence indicates that the mGlu2 receptor plays an important role in regulating the dopaminergic system both presynaptically and postsynaptically (Morishima et al., 2005). Thus, pharmacological studies have shown that mGlu2 receptors inhibit pyramidal neurons postsynaptically in the PFC and presynaptically in the NAcc (Morishima et al., 2005). Hence, the lack of mGlu2 receptors may result in a reduced inhibition of pyramidal neurons in both the PFC and the NAcc, thereby leading to an increased release of glutamate in the NAcc (Morishima et al., 2005) (Figure 1). It may be postulated that the increased extracellular concentration of glutamate can stimulate NMDA receptors at the presynaptic terminals of DA neurons in the NAcc, inducing further increments in DA concentrations in the synaptic cleft and leading to a stable enhancement of the functional tone of the mesolimbic DA system. This hypothesis is consistent with the enhanced vulnerability to sensitization induced by drugs of abuse or with the increased density of D1 receptors in the PFC and NAcc of RHA rats (Elfving et al., 2019; Giorgi et al., 1994, 2007; Guitart-Masip et al., 2006).

The mGlu2 receptors are involved in LTD-related synaptic plasticity in the HC and the AMY (Lucas et al., 2013), and also in synaptic pruning during adolescence (Selemon, 2013). Therefore, the disruption of the normal maturation of the HC (and perhaps other limbic regions, such as the AMY), due to the lack of mGlu2 receptors in RHA rats (Elfving et al., 2019; Fomsgaard et al., 2018; Klein et al., 2014), may also facilitate the sensitization of DA systems to addictive substances. Accordingly, in the NVHL model, the neonatal lesion of the ventral hippocampus prevents the normal maturation of the HC and elicits a broad spectrum of schizophrenia-related phenomena that become apparent in the postpubertal period, some of which are ameliorated by antipsychotics (e.g. Corda et al., 2006; Tseng et al., 2009). Interestingly, among other schizophrenia- and addiction-relevant features, the NVHL model shows, similar to RHA rats, enhanced locomotor and DAergic sensitization following chronic administration of psychostimulants (Corda et al., 2006; Tseng et al., 2009). Another important parallelism with the RHA model is that in the NVHL model the density of 5-HT_{2A} receptors is elevated in the PFC (Mitazaki et al., 2020; Fomsgaard et al., 2018; Klein et al., 2014), although mGlu2 receptors have not been measured in NVHL rats. Hence, both the RHA and NVHL models appear to have

in common some alterations of dopamine and serotonin transmission that are likely involved in certain schizophrenia-related features.

As postulated for the NVHL model, the anomalous hippocampal maturation in RHA rats (linked to their deficit of mGlu2 receptors) would alter the normal regulation of GABA interneurons by the mesocortical DA pathway in the PFC (Tseng et al., 2009, and references therein). HC disruption in the NVHL model leads to post-pubertal anomalous NMDA- and D1-mediated activation of prefrontal cortical pyramidal neurons and GABAergic interneurons (Tseng et al., 2009, and references therein), which might be related to the altered excitation/inhibition balance observed in NVHL rats (Tseng et al., 2009). Consistent with these findings from the NVHL model, RHA rats present a decreased volume and task-induced activity of the HC and the PFC (Meyza et al., 2009; Río-Álamos et al., 2019; Sallés et al., 2001; Tapias Espinosa et al., 2019), prefrontal cortical increases of NMDA and D1 receptors (Elfving et al., 2019), and a reduced PPI-induced activity of (PV+) GABAergic interneurons in the PFC (Tapias-Espinosa 2020), all of which are compatible with an altered excitation/inhibition balance in the PFC.

Thus, early alterations of hippocampal development and synaptic processes in RHA rats, driven by the lack of mGlu2 receptors, may affect the normal development of brain regions and systems that mature later in adolescence, such as the PFC and its DA /glutamate/GABA (and thus, inhibitory/excitatory) functional balance. It may be proposed that the early disruption of the HC is crucial for the generation of the frontocortical phenotypes observed in adult RHA rats (e.g., hypofrontality; Meyza et al., 2009; Río-Álamos et al., 2019; Tapias-Espinosa et al., 2019). This process bears resemblance to what is considered to occur in the NVHL model (e.g. Corda et al., 2006; Tseng et al., 2009), and further longitudinal/developmental studies are warranted to establish whether this is indeed the case in the RHA model.

3.1. Summary and hypothetical scheme

Summarizing and simplifying, the main aspects of our neurodevelopmental glutamate-based hypothesis, concerning the schizophrenia- and addiction-relevant anomalies that the RHA model exhibits, can be formulated as follows (see Figure 2):

Glutamate-mediated synaptic plasticity is involved in synaptic pruning and dendritic spine maturation during neurodevelopment. Therefore, the lack of mGlu2 receptors (due to the cys407* mutation) in PFC, HC and STR of RHA rats, and thus the alterations of the 5-HT2A/mGlu2 receptor complex function, could lead (or might be related) to a series of associated neurodevelopmental processes, such as:

(i)- Alterations in prefrontal (and hippocampal) BDNF system, which shows functional interactions with mGlu2 receptors, and may lead to altered plastic and synaptic neurodevelopmental processes.

(ii)- Synaptic alterations at PSD, such as Homer1 and Nrg1, which are involved in glutamatergic, dopaminergic and serotonergic signaling, and in the regulation of excitatory/inhibitory neurotransmission.

(iii)- These altered levels of Homer1, Ngr1 and BDNF, that are known to be important regulators of dendritic spine morphogenesis and density, are likely related to synaptic alterations in the PFC of RHA rats.

(iv)- In fact, in the PFC of RHA rats there is up-regulation of some core presynaptic markers of the SNARE complex, which regulates glutamate NMDA receptor-linked processes.

(v)- Consistently, an increased density of immature ("thin") dendritic spines (which are known to express NMDA receptors) is observed in the PFC of RHA rats.

(vi)- There is an increased number of astrocytes in the PFC of RHA rats. Given their important role in the maturation of excitatory synapses, such an increased number of astrocytes is likely associated with the dendritic spine alterations in this rat strain. Alterations in astrocyte regulation of glutamate release in the PFC, through activation of their mGlu2/3 receptors, and thus altered NMDA receptor activation may contribute to these anomalies in dendritic spines.

(vii)- There are alterations of NMDA receptor activation in the PFC, also linked to altered GABA interneuron activity in the PFC of RHA rats, which in turn might be linked to disrupted Nrg1/ErbB4 signaling in these GABA neurons. Such disruption of Nrg1/ErbB4 signaling may be involved in dendritic spine destabilization and glutamatergic disfunction.

(viii)- GABA interneurons in the PFC receive dopaminergic innervation from the ventral tegmental area (VTA) and express D1 and D2 receptors. D1 receptors are involved in NMDA receptor trafficking to postsynaptic membranes. Both D1 and NMDA2B receptors show increased density in PFC of RHA rats.

(ix)- Hence, there is likely an altered excitatory (glutamate-linked)/inhibitory (GABA-linked) balance in the PFC of RHA rats, and impaired top down inhibitory control (Figure 1, Figure 2).

(xi)- Consistent with the above is the decreased function of PFC and HC in RHA rats, likely related to a poor top down inhibitory control (Figure 1, Figure 2) and, specifically, to their deficit of impulse control, as well as attentional, cognitive and social behavior impairments.

(xii)- Such an impaired top down inhibitory control is likely related to the increased mesolimbic dopaminergic functional tone in RHA rats, increased behavioral and dopaminergic sensitivity to acute and chronic psychostimulants (and other drugs of abuse), impaired sensorimotor gating (that initiates during adolescence), and behavioral disinhibition (i.e. increased locomotor activity) that is already present at pre-puberty and early puberty in the RHA model (Figure 1, Figure 2).

In sum, it is hypothesized that the lack of mGlu2 receptors (and thus the alteration of 5-HT2A/mGlu2 receptor complex function) in RHA rats may underlie a cascade of processes leading to neurodevelopmental alterations that finally shape a number of neural and behavioral phenotypes that collectively resemble an immature/adolescent stage of brain development in these rats. These traits are consistent with a neurodevelopmental view of schizophrenia-relevant features and drug addiction-related phenomena.

4. Concluding remarks and perspectives

Genetically-derived rat models based on selective breeding for specific phenotypic differences have received much less attention than genetically-engineered rodent models, i.e. gene targeting approaches such as transgenic or knockout mice. These gene targeting models constitute etiology-focused strategies (i.e. if a gene is manipulated and produces consequences in a given phenotype, then the gene is considered to be one possible “cause”

underlying that trait). Notably, however, the etiological hypotheses are the main constraints of these models. One of their limitations stems from their frequently applied single-mechanism approach, which usually disregards many other possibly relevant neurobiological, neurodevelopmental, genetic, epigenetic, and environmental factors or processes that may be germane to the target phenotype/disease. This is especially true when dealing with complex multifaceted, multicausal and neurodevelopmental polygenic syndromes or traits, such as schizophrenia or its associated symptoms (e.g. Ayhan et al., 2016; Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014; Flint and Munafo 2014). A complementary and more ethologically oriented approach, which can overcome these limitations of gene targeting approaches, would be to use top-down "behavior-to-biology" models, such as animals selectively bred for their values in a given quantitative phenotype (of which the Roman rats are an example). These approaches, similarly to the strategy used by human "genome wide association studies" (GWASs), rather than assuming a given pathophysiological mechanism (as do gene targeting approaches) take advantage of the quantitative phenotypic (or trait) variation to study its association with "normal" genotypic variation to find "candidate quantitative genes". One advantage of gene targeting approaches is the possibility of controlling for genetic/epigenetic processes, since littermates can be used as controls. This is not possible when using selectively bred strains, although (i) comparison of these strains with other (as many as possible) standard laboratory strains, and (ii) systematic phenotypic evaluation and comparison of sub-strains established at different locations, may mitigate that problem of "controls". For example, it is noteworthy that the main (avoidance, emotional, cognitive, endocrine, addiction- and schizophrenia-related) traits/phenotypes differentiating RHA vs RLA rats have been maintained across different laboratories (Spain, Italy, Switzerland, Germany, France, England, USA; see Table S1). On the other hand, compared with gene targeting models, studies based on the selective breeding for particular phenotypes (or even stratification for quantitative phenotypes without carrying out selective breeding) present the unique advantage of allowing to carry out quantitative genetics (i.e. GWAS-like) studies, which in turn allow identification of multiple quantitative trait genes in the same study (e.g. Baud et al., 2013, 2014a,b; see Table S1 for other quantitative genetic studies based on selectively bred rats).

Regarding the Roman rats, one such quantitative genetics study (in an approach similar to GWASs) pioneered bringing glutamatergic neurotransmission to the scene in relation

to genetic differences between the RHA and RLA strains. Thus, using > 800 F2 rats (hybrids of RHA and RLA strains), we reported a "quantitative trait locus" (QTL) in chromosome 5 influencing two-way avoidance acquisition and other phenotypes related to cognition (i.e. pavlovian aversive conditioning), locomotor activity, risk taking and self-grooming (Fernandez-Teruel et al., 2002b). Further fine-mapping of this QTL revealed that it contained only 9 genes (Johannesson et al., 2009), one of which is the *Mpdz* (Multiple PDZ domain protein) gene, a member of the NMDA receptor signaling complex that seems to be involved in control of AMPA receptor potentiation and synaptic plasticity, and has also been associated with 5-HT2C and possibly GABA-B receptor function. *Mpdz* is currently considered as a quantitative trait gene influencing alcohol comsumption and withdrawal (e.g. Metten et al., 2014; Milner et al., 2015), and some effects of opiates (Donaldson et al., 2016). Although no further characterization of the *Mpdz* gene has been carried out in the Roman rat strains, this gene would deserve further exploration, given that: (i) it appears to connect glutamate, serotonin and maybe GABA activities, and (ii) RHA and RLA rats markedly differ in their sensitivity to, and preference for ethanol and other abused drugs, and in the effects of NMDA receptor antagonists.

The complexity of the genetic mechanisms associated with schizophrenia was in fact highlighted by a recent metanalysis of GWAS studies carried out by the Psychiatric Genomics Consortium (PGC), which identified 108 loci that contribute to risk for the disorder. Studying 37,000 patients with schizophrenia and 113,000 healthy controls the consortium identified 83 novel risk markers and replicated 25 existing markers, among which genes involved in neurodevelopment, the immune and stress response, glutamatergic neurotransmission, and DA D2 receptors stand out. It is interesting that, particularly regarding neurodevelopmental aspects, glutamate and DA neurotransmission, this study by the consortium shows striking coincidences with what we have discussed about RHA (vs RLA) rats in the present article.

There is considerable consensus that in order to understand the neurogenetic bases of schizophrenia we will need to work with models that take into account gene-environment interactions. Thus, for instance, interactions between genetic risk and environmental stressors or factors modulating experience-dependent plasticity –in interaction with ontogeny- are generally thought to be of great importance in the development of the disorder (e.g. Burrows and Hannan 2016; Laviola et al., 2009; Moran et al., 2016;

Nimgaonkar et al., 2017). In this regard, as mentioned earlier in this article, we have reported genotype-environment effects of (stressful) isolation rearing and RHA genotype on emotional, cognitive and attentional phenotypes (Oliveras et al., 2016; Sanchez-González et al., 2019), as well as of neonatal handling and RHA genotype on emotional responses, sensotimotor gating (PPI), cognitive flexibility, social behavior and hippocampal volume (Río-Álamos et al., 2017b, 2019; Sampedro-Viana et al., 2021). Ongoing studies are focused on exploring the genetic/epigenetic underpinings of some of these genotype-environment interactions in the RHA vs RLA rats.

The RHA model constitutes the first genetically-based (selectively-bred) rat model of schizophrenia-relevant features having a mutation that precludes the presence of mGlu2 receptors. This, as seen in the present review, may have relevant implications for the research on the relationship between glutamate and 5-HT, GABA and DA transmission, as well as for the neurodevelopmental effects related to mGlu2 receptors and their role in schizophrenia- and addiction-related features. On the other hand, it is worth noting that, relative to RHAs and other rat strains/stocks, RLA rats appear to be resistant to locomotor and mesolimbic sensitization induced by chronic treatments with psychostimulants, morphine or alcohol, while apparently exhibiting traits of good PFC- and HC-related inhibitory control as well as of good attentional/cognitive traits and resistance to the deleterious effects of isolation rearing. Altogether, these findings suggest that RLA rats may represent a valid model of resistance to both substance abuse and developmentally-induced schizophrenia-related phenotypes (Figure 1).

Turning back to the RHA model, it can be said that it presents reasonable face validity, as shown by increased locomotor activity, decreased social behavior, impairments in attention and cognitive processes, deficits induced by social isolation rearing, enhanced sensitivity to (acute and chronic) psychostimulant effects and vulnerability to drug sensitization and addiction. The predictive validity of the model also seems reasonable, and relies in the observed differential (RHA vs RLA) effects of psychostimulants (amphetamine, apomorphine, cocaine) and some antipsychotic (haloperidol, clozapine, ziprasidone, aripiprazole, oxytocin) and propsychotic drugs (dizocilpine, DOI), observed on PPI, dizocilpine-induced hyper-locomotion, or dizocilpine-impaired social interaction preference. Other antipsychotic (and putative antipsychotic) drugs, other administration regimes and other tasks, for instance, will be necessary to get further insight on the predictive validity of the model.

The described alterations of the 5-HT2A/mGlu2 receptor complex and the mesocorticolimbic dopaminergic characteristics, together with the aforementioned changes in pre- and post-synaptic markers, dendritic spines, trophic factors, 5-HT and NMDA receptors, and PFC and HC hypofunction in RHA rats (Figure 1-2), seem to provide them some construct validity as a neurodevelopmental model of schizophrenia- and drug addiction-related traits. In this regard, in order to explore further the involvement of the mGlu2-related mutation in the neurobehavioral profile of RHA rats, it would be interesting to study whether restoring the expression of mGlu2 receptors (using virally mediated over-expression, for instance; see Hideshima et al., 2018) in the PFC and/or HC could contribute to "normalize" some of their characteristic behavioral, neural and/or pharmacological profiles.

The reviewed evidence strongly suggests a more immature state of the PFC (and probably the HC) in the RHA rats, which may underlie their schizophrenia- and addiction-related neurobiological traits. Current and future studies of our group are aimed at performing a transcriptomic analysis and look for enrichment of gene pathways related to neurodevelopment (i.e. differential expression of functional gene modules differentially regulated during childhood and early adolescence) in RHA rats. Only a few studies have previously looked at gene expression profiles in these rat strains (Sabariego et al., 2011, 2013). These were though microarray based studies, that do not have the same coverage as transcriptomics approaches. Still, among the differential expressed genes, 14 up-regulated and 24 down-regulated in RLA vs. RHA rats, they found enrichment in processes related to neurodevelopment and function (Sabariego et al., 2011). In the second study, they found, after exposing both strains to a frustrative experience involving reward downshift, differential gene expression in the hippocampus of genes involved in cellular growth and proliferation and synaptic function (Sabariego et al., 2013). More studies are needed exploring more in detail the differences in gene expression profile between these two strains in PFC areas and relate them to neurodevelopment and executive function maturation. Based on these previous studies we expect this to be quite extensive.

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Figure 1

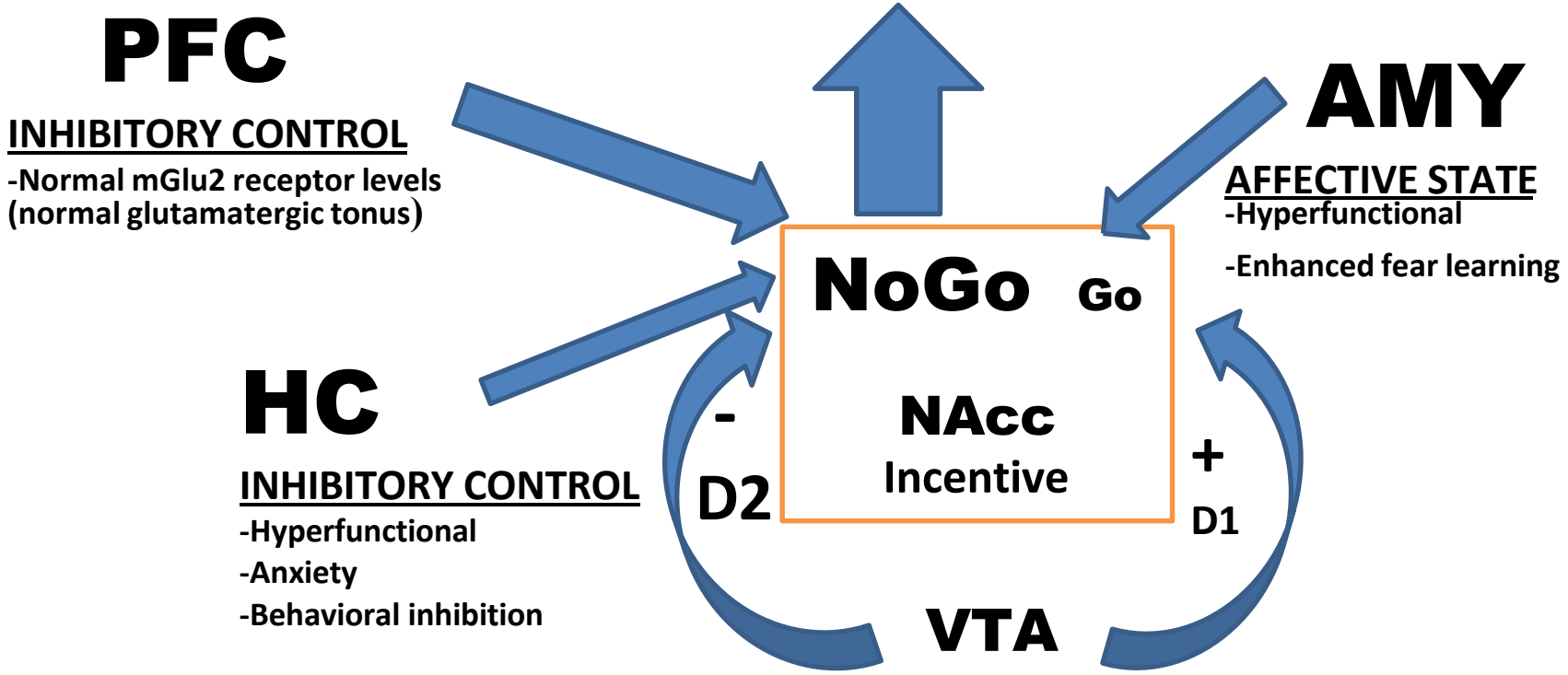
RLA rats

A

BEHAVIORAL INHIBITION

-Resistance to psychostimulant sensitization and to drug addiction

-Normality regarding schizophrenia-relevant traits: good PPI and LI, good spatial and working memory, good cognitive flexibility, normal social behavior, resistant to MK801-induced impairment of social preference and hyperactivity, impulse control.



RHA rats

B

PFC

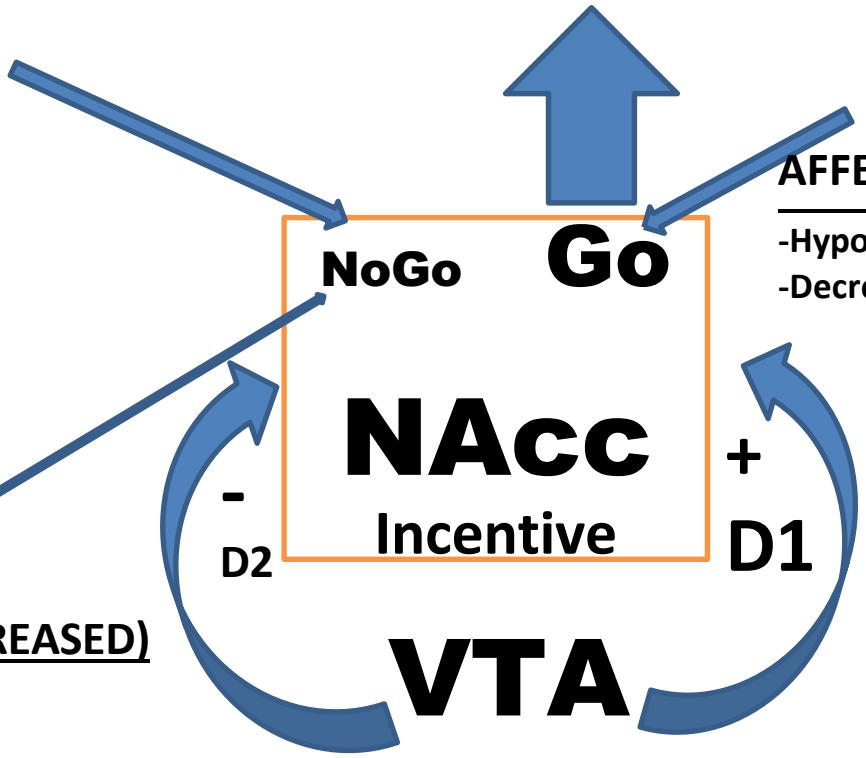
INHIBITORY CONTROL (DECREASED)

-Hypofunctional state/ Hypofrontality
-Decreased mGlu2 receptors
(disrupted glutamatergic transmission)
-Increased 5-HT2A receptors
(enhanced impulsivity)
-Increased BDNF
-Increased Homer 1
-Increased Neuregulin 1
-Altered pre-synaptic markers

-Increased NMDA2B receptors
-Increased D1 receptors
-Increased astroglia number
-Increased density of immature ("thin")
pyramidal dendritic spines
-Decreased activity of GABA interneurons
-Disrupted excitation/inhibition balance

BEHAVIORAL DISINHIBITION

-Impulsivity / Sensation-novelty seeking
-Schizophrenia-like positive symptoms, negative symptoms (asociality) and attentional/cognitive impairments (e.g. PPI, LI, starle habituation, working memory)
-Enhanced NMDA antagonist-induced hyperactivity and impairment of social interaction preference
-Enhanced psychostimulant sensitization
-Vulnerability to drug abuse/addiction



AMY

AFFECTIVE STATE

-Hypofunctional
-Decreased fear learning

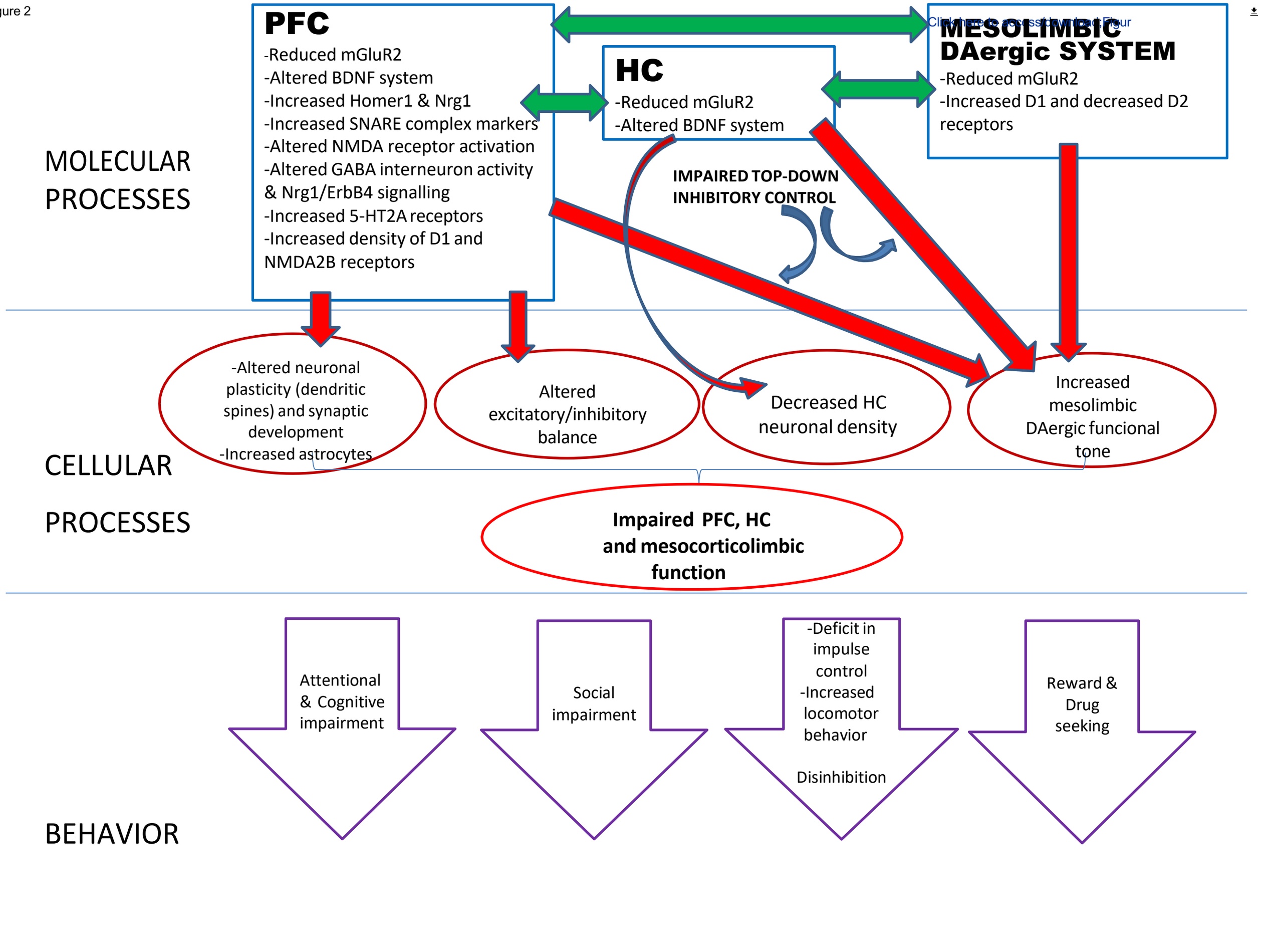
HC

INHIBITORY CONTROL (DECREASED)

-Hypofunctional state
-Decreased mGlu2 receptors
-Decreased anxiety
-Behavioral disinhibition
under conflict

- **Legend to Figure 1.-** Simplified model of the functions of the mesocorticolimbic dopaminergic circuit and its modulation by limbic and frontocortical areas in relation to their differential involvement in behavioural inhibition/disinhibition, impulsivity, schizophrenia-like features, and drug seeking/addiction in RHA and RLA rats. In this schematic diagram the arrow thickness and character size represent the intensity of the functional tone or the receptor (or marker) density of the corresponding brain area or neural circuit, respectively. The lower neuronal activity and volume of the mPFC, the HC, and the AMY, the increased density of 5-HT2AR and the absence of mGlu2R, together with the alterations of BDNF, Homer1, Neuregulin 1, NMDA2B and D1 receptors, and pre-synaptic markers in RHA vs. RLA rats, is consistent with the possibility of a hyper- functional glutamatergic cortical system that would in turn lead to an increased functional tone of the mesolimbic dopaminergic system and a decreased functional tone of the meso-cortical dopaminergic system in RHA rats. These alterations of synaptic markers, trophic factors and GABA interneuron function in the PFC are also consistent with the increased density of immature ("thin") pyramidal dendritic spines and astroglia in RHA rats, which collectively characterize an immature PFC (and, likely, HC), and thus an altered excitation/inhibition balance and a disrupted top down inhibitory control. Collectivelly, the lowered function of the PFC, the HC, and the AMY, along with the increased functional tone of the mesolimbic dopaminergic system of RHA rats favour behavioral disinhibition, impulsive actions/responses, attentional/cognitive deficits and vulnerability to drug addiction. Abreviations: PFC, prefrontal cortex; HC, hippocampus; AMY, amygdala; NAcc, nucleus accumbens; VTA, ventral tegmental area; mGlu2R, metabotropic glutamate type 2 receptors; 5-HT2AR, serotonin type 2A receptors; D2, dopamine type 2 receptors; D1, dopamine type 1 receptors; PPI, prepulse inhibition; LI, latent inhibition; NMDA, N-metyl-D-aspartate receptor; BDNF, brain-derived neurotrophic factor; GABA, gamma aminobutyric acid (see text).

Figure 2


PFC
-Reduced mGluR2
-Altered BDNF system
-Increased Homer1 & Nrg1
-Increased SNARE complex markers
-Altered NMDA receptor activation
-Altered GABA interneuron activity & Nrg1/ErbB4 signalling
-Increased 5-HT2A receptors
-Increased density of D1 and NMDA2B receptors
HC
-Reduced mGluR2
-Altered BDNF system
MESOLIMBIC DAergic SYSTEM
-Reduced mGluR2
-Increased D1 and decreased D2 receptors
IMPAIRED TOP-DOWN INHIBITORY CONTROL
MOLECULAR PROCESSES
-Altered neuronal plasticity (dendritic spines) and synaptic development
-Increased astrocytes
Altered excitatory/inhibitory balance
Decreased HC neuronal density
Increased mesolimbic DAergic funcional tone
CELLULAR PROCESSES
Impaired PFC, HC and mesocorticolimbic function
BEHAVIOR
Attentional & Cognitive impairment
Social impairment
-Deficit in impulse control
-Increased locomotor behavior
Disinhibition
Reward & Drug seeking

Legend to Figure 2.-

Main molecular, cellular and behavioral alterations in the RHA rat model of schizophrenia- and drug addiction-relevant features.

Green arrows indicate “interaction”. Red arrows indicate “alteration” or“impairment”.
See text for abbreviations in Fig. 1 and text.

Table 1

Table 1.- Main behavioral phenotypes related to schizophrenia, addiction and impulsivity in treatment-naïve RHA rats.

Related pathology	Behavioural phenotype	Effects of RHA genotype (vs RLA, Wistar or Wistar--derived, Sprague Dawley, HS rats, and other strains/stocks)	Representative references
Schizophrenia			
	Locomotor activity (baseline) *	Higher locomotor activity in treatment-naïve RHA rats in various novelty-based tests (vs. RLA and outbred HS rats)	Escorihuela et al., 1997, 1999; Estanislau et al., 2013; Fernández-Teruel et al., 1991a, 1992a, 1993; Gentsch et al., 1981, 1991; Gimenez-Llort et al., 2005; Tapias-Espinosa et al., 2018; Oliveras et al., 2016, 2017; Driscoll et al., 2009
	Latent Inhibition (LI)	RHA rats have impaired latent inhibition, in the two-way active avoidance and fear-potentiated startle paradigms, relative to Sprague-Dawley and RLA rats	Fernández-Teruel et al., 2006; Esnal et al., 2016
	Prepulse inhibition (PPI) *	RHA rats have impaired PPI compared to RLA and genetically-heterogeneous (outbred) HS rats	Del Río et al., 2014; Oliveras et al., 2015; 2016; Río-Álamos et al., 2015, 2017a-b, 2019; Tapias-Espinosa et al., 2018, 2019
	Habituation of acoustic startle response *	RHA rats show decreased startle habituation compared with RLAs	Aguilar et al., 2000; Rio-Alamos et al., 2015
	Maternal behavior (nursing/nesting)	RLA mother rats are more protective of their litters than RHA mothers	Driscoll et al., 1979, 1991; Del Río et al., 2014
	Social preference (drug-naive) *	Impaired social preference (SP) of the RHA rats relative to RLA and outbred HS rats (RHA, 50 % SP; RLA, 70 % SP; HS, 70%)	Sampedro-Viana et al. (2021); Lavín 2019; Torrecilla 2018

Table 1 (continued)

Spatial reference learning/memory in the Morris water maze	RHA rats show impaired spatial reference memory relative to RLA and outbred HS rats	Aguilar et al., 2002a; Driscoll et al., 1995; Escorihuela et al., 1995b; Martínez-Membrives et al., 2015; Oliveras et al., 2016; Río-Álamos et al., 2019
Spatial working memory in the Morris water maze	RHA rats show impaired working memory compared with RLA and outbred HS rats	Aguilar et al., 2002a; Oliveras et al., 2015, 2016; Río-Álamos et al., 2019
Reversal place learning (cognitive flexibility) in the Morris water maze	RHA rats show impaired cognitive flexibility (i.e. impaired performance in the reversal place task) relative to RLA rats	Río-Álamos et al., 2019, Escorihuela et al., 1995b
Non-spatial and spatial reference and working memory (delayed alternation, radial maze, novel object discrimination)	RHA rats are impaired in these tasks relative to RLA rats and to control (Wistar-derived) RCA rats	Guenaire et al., 1986; Guenaire and Delacour 1985; Willig et al., 1991a-b, 1992
Efficiency of hexagonal tunnel maze patrolling/exploration and Hebb-Williams water maze learning *	RHA rats explore the tunnel maze less efficiently than do RLA rats and show impaired learning of most of the configurations of the Hebb-Williams maze	Duetsch and Bättig, 1977; Driscoll and Bättig 1982; Nil and Bättig, 1981
Context-conditioned suppression of drinking or activity, and context- and cue-conditioned freezing *	RHA rats exhibit reduced context (pavlovian)-conditioned suppression and decreased context-and cue-conditioned freezing (compared with RLA and outbred HS rats)	Guenaire et al., 1986; Escorihuela et al., 1997; Fernandez-Teruel et al., 1998; Imada 1972; Lopez-Aumatell et al., 2009a

Table 1 (continued)

Addiction, novelty/reward-seeking			
	Novelty-induced locomotion *	Increased in RHA rats relative to RLA and outbred HS rats	Diaz-Moran et al., 2012, 2013; Escorihuela et al., 1997, 1999; Estanislau et al., 2013; Fernandez-Teruel et al., 1991a-b, 1992a-b; Gentsch et al., 1981; Tapias-Espinosa et al., 2018
	Sensation/novelty seeking *	Increased in RHA relative to RLA and outbred HS rats	Estanislau et al., 2013; Fernández-Teruel et al., 1992b, 1997; Pisula, 2003; Tournier et al., 2013
	Preference for natural rewards	Increased in RHA relative to RLA rats	Giorgi et al., 2019; Sanna et al., 2014a, 2017, 2019
	Drug-seeking and operant behavior for intravenous drug self-administration	Increased in RHA vs. RLA rats in both the two-bottle free choice (ethanol) procedure and operant intravenous self-administration (cocaine)	Corda et al., 2014; Dimiziani et al., 2019; Fattore et al., 2009; Fernández-Teruel et al., 2002a; Manzo et al., 2012, 2014a-b, 2015; Razafimanalina et al., 1996
Impulsivity			
	5-choice serial reaction time task (5-CSRTT)	RHA rats exhibit increased impulsive (i.e. premature) responses relative to RLA rats	Moreno et al., 2010; Klein et al., 2014; Merchan et al., 2019; Bellés et al., 2021
	Delay discounting operant task	Enhanced impulsivity of RHA rats in the delay-discounting task, compared to RLA rats	Moreno et al., 2010

Table 1 (continued)

Scheduled-induced polydipsia	Increased impulsivity (i.e. increased amount of water drunk) in RHA relative to RLA rats	Moreno and Flores 2012; Moreno et al., 2010; Merchán et al., 2019
Unpredictable instrumental conditioning	Increased impulsivity in RHA relative to RLA rats	Coppens et al., 2012, 2013
Learning an instrumental DRL20 task *	Impaired learning, due to deficient inhibition of irrelevant responses (i.e. to increased impulsivity), in RHA (vs. RLA rats)	Zeier et al., 1978

***,** indicates that these studies (or some of them) used females or males and females; otherwise the studies were carried out with males. See abbreviations

Table 2

Table 2.- Main psycho- and neuro-pharmacological phenotypes related to schizophrenia and addiction in RHA rats.

Related pathology	Psychopharmacological phenotype	Effects of RHA genotype (vs RLA and, in some cases, Sprague Dawley or outbred HS rats)	Main references
Related to schizophrenia & drug addiction			
	Apomorphine-induced stereotypies	More intense stereotypies in RHA than RLA rats	Driscoll et al., 1985; Gimenez-Llort et al., 2005
	Locomotor activity or stereotypies after acute amphetamine or cocaine	Higher locomotor activity or stereotypies in RHA than RLA rats	Corda et al., 2005 Driscoll et al., 1986; Haney et al., 1994; Lecca et al., 2004. See reviews by Giorgi et al., 2007, 2019
	Chronic amphetamine-induced locomotor sensitization	More intense locomotor sensitization In RHA rats than in RLA and Sprague Dawley rats	Corda et al., 2005; reviewed by Giorgi et al., 2007; Guitart-Masip et al., 2008a; Tournier et al., 2013
	Locomotor activity after acute cocaine	Higher locomotor activity in RHA than RLA rats	Giorgi et al., 1997, 2005a, 2007; Lecca et al., 2004
	Chronic cocaine-induced locomotor sensitization	More intense sensitization in RHA than RLA rats	Giorgi et al., 2005a, 2007
	Locomotor activity after acute morphine	Higher locomotor activity in RHA than RLA rats	Piras et al., 2003; Lecca et al., 2004
	Chronic morphine-induced locomotor sensitization	More intense locomotor sensitization in RHA than RLA rats	Piras et al., 2003; Giorgi et al 2007

Table 2 (continued)

Haloperidol-induced hypoactivity	Less intense hypoactivity induced by acute haloperidol in RHA than RLA rats	Oliveras et al., 2017
Haloperidol effect on PPI	RHA (but not RLA) rats acutely treated with haloperidol improved PPI performance	Oliveras et al., 2017
Apomorphine effect on PPI	RHA (but not RLA) rats acutely treated with apomorphine show impaired PPI	Oliveras et al., 2017
Oxytocin effect on PPI	RHA (but not RLA) rats acutely treated with oxytocin improved PPI performance by 18 % compared to the respective vehicle-treated group (outbred HS rats were also included for comparison)	Tapias-Espinosa 2020; Tapias-Espinosa et al., 2021
Dizocilpine-induced increase of locomotor activity and impairment of PPI	Acute dizocilpine (dose-dependently) enhances locomotor activity more markedly in RHA rats than in RLA rats. Acute dizocilpine impairs PPI to a similar extent in RHA and RLA rats	Oliveras et al., 2017; Torrecilla 2018
Clozapine, aripiprazole and ziprasidone effects on dizocilpine-induced locomotor hyperactivity	Clozapine, aripiprazole and ziprasidone attenuate dizocilpine-induced hyperactivity more effectively in RHA than in RLA rats	Oliveras et al., 2017; Lavín 2019
Oxytocin effect on dizocilpine-impaired social preference	Moderate attenuation of dizocilpine (0.15 mg/kg)-induced impairment of social preference in RHA rats treated with oxytocin 0.04 and 0.2 mg/kg. No effect in RLA rats	Ancil-Gascón 2020

Table 2 (continued)

Oxytocin effect on dizocilpine-induced locomotor hyperactivity	Moderate attenuation of dizocilpine (0.15 mg/kg)-induced locomotor hyperactivity in RHA rats treated with oxytocin 0.04 and 0.2 mg/kg. No significant effect in RLA rats	Ancil-Gascón 2020;
Dizocilpine-impaired social preference	A dose-related reduction of social preference in dizocilpine-treated RHA rats (> 60% reduction with the highest dose, 0.2 mg/kg) relative to the vehicle-treated group (no effect on social preference in RLA rats)	Torrecilla 2018; Lavín 2019
Clozapine, ziprasidone and aripiprazole effects on dizocilpine-induced impairment of social preference	Attenuation (clozapine) or reversal (ziprasidone, aripiprazole) of dizocilpine (0.15 mg/kg)-induced impairment of social preference in RHA rats. No effect in RLA rats	Lavín 2019

Table 2 (continued)

Related to addiction, reward seeking & dopaminergic mesolimbic involvement			
	Psychostimulant (amphetamine, cocaine)-sensitized mesolimbic dopamine efflux	Increased in RHA relative to RLA rats (NAcc core)	Giorgi et al. 2005b, 2007, 2019; Lecca et al., 2004
	Amphetamine (AMPH)-induced DA release in striatum (dorsal and ventral)	Enhanced AMPH-induced DA release in striatum, which correlates with impulsive behavior, in RHA relative to RLA rats	Bellés et al., 2021
	Morphine-sensitized mesolimbic dopamine efflux	Increased in RHA relative to RLA rats (NAcc core)	Lecca et al., 2004; Giorgi et al., 2007
	Chronic ethanol drinking/preference and chronic ethanol-induced accumbal dopamine efflux	Both increased in RHA relative to RLA rats	Corda et al., 2014
	Sexual motivation and sexual activity, and mesocorticolimbic dopaminergic function	Increased sexual motivation and sexual activity in RHA relative to RLA and Sprague Dawley rats, and increased dopamine efflux in NAcc shell and mPFC during sexual activity in the former strain	Sanna et al., 2013, 2014a,b; 2015

Table 2 (continued)

	Apomorphine and haloperidol effects on sexual activity	Apomorphine-induced facilitation and haloperidol-induced impairment of copulatory behaviour were more robust in RLA than RHA rats	Sanna et al., 2014b

See abbreviations in the text.

Table 3

Table 3.- Main neuroanatomical, functional and molecular phenotypes related to schizophrenia in RHA rats.

Neurobiological Phenotype		RHA vs. RLA rats	Main references
Neuroanatomical and functional schizophrenia-relevant phenotypes of RHA rats: comparison with RLA rats			
	Prefrontal cortex (PFC)	Decreased volume and neuronal activity (c-fos), and increased density of pyramidal dendritic "thin" (immature) spines and astroglia number in RHA rats	Meyza et al., 2009; Río- Álamos et al., 2019; Tapias- Espinosa et al., 2019; Sánchez-González et al., 2019, 2021
	Nucleus Accumbens (NAcc)	No difference in volume between RHA and RLA rats	Giorgi et al., 2007; Río- Álamos et al., 2017b, 2019; Tapias- Espinosa et al., 2019
	Hippocampus (HPC)	Decreased volume, neuronal density and function (c-fos) in RHA rats	Garcia-Falgueras et al., 2012; Meyza et al., 2009; Río-Álamos et al., 2017b, 2019; Sallés et al., 2001; Tapias-Espinosa et al., 2019; Sánchez-González et al., 2019
	Amygdala (AMY)	Decreased volume, neuronal density and function (c-fos) in RHA rats	Gomez et al., 2009c; Meyza et al., 2009; Río- Álamos et al., 2017b, 2019; Tapias-Espinosa et al., 2019
	Striatum volume	No between-strain difference	Río-Álamos et al., 2017; Tapias-Espinosa et al., 2019; Sánchez-González et al., 2019

Table 3 (continued)

	Anterior Cingulate volume	No between-strain difference	Río-Álamos et al., 2019; Tapias-Espinosa et al., 2019
	Volume of lateral ventricles	Much larger (2-fold) in RHA rats	Río-Álamos et al., 2017b, 2019
	Activation of parvalbumin (PV)-labelled GABA interneurons in prefrontal cortex following a PPI session	RHA rats exhibit an approximately 60% reduced activation (measured by c-fos) of GABA (PV-labelled) interneurons relative to RLA rats	Tapias-Espinosa 2020
Neurochemical/molecular phenotypes			
	Dopamine (DA)	Increased mesolimbic functional dopaminergic tone in RHA rats	Giorgi et al., 2007, 2019; Tournier et al., 2013
	Dopamine D1 receptors	Increased density in limbic areas and increased mRNA expression in PFC of RHA rats	Giorgi et al., 1994, Guitart-Masip et al., 2006; Elfving et al., 2019
	Dopamine D2 receptors	Decreased density in limbic areas in RHA rats	Guitart-Masip et al., 2006; Tournier et al., 2013
	Dopamine D3 receptors in NAcc	Increased in RHA rats	Guitart-Masip et al., 2006
	Dopamine D3 receptors in Calleja Islands	Decreased in RHA rats	Guitart-Masip et al., 2006
	Noradrenaline (NA)	Increased NA levels and release in the PFC of RHA rats	Sanna et al., 2017

Table 3 (continued)

Serotonin (5-HT)	Increased levels in the cortex (after MAO inhibition) in RHA rats. Increased release in PFC of RHA rats	Driscoll et al., 1980; Giorgi et al., 2003b
5-HT receptors	Increased fronto-cortical [3H]-paroxetine and [3H]-citalopram receptor binding in RHA rats. Increased 5-HT2A receptor density in PFC of RHA rats	Charnay et al., 1995; Foomsgard et al., 2018; Giorgi et al., 2003b; Klein et al., 2014
mGlu2 receptors	Dramatic reduction in PFC, HC and striatum of RHA rats	Elfving et al., 2019; Kein et al., 2014; (see Wood et al., 2017)
NMDA receptors	Increased NMDA2B receptors in PFC of RHA rats	Elfving et al., 2019
BDNF	Increased expression in PFC of RHA rats	Elfving et al., 2019; Sanna et al., 2019
Neuroregulin 1	Increased expression in PFC and increased protein levels in HC of RHA rats	Elfving et al., 2019
Homer1	Increased expression in PFC of RHA rats	Elfving et al., 2019
Pre-synaptic markers	Altered SNARE complex proteins in PFC and HC of RHA vs RLA rats	Elfving et al., 2019

See abbreviations in text.

Supplementary Table 1 (continued)

Table S1

Supplementary Table 1 (S1).- Main contributions from different groups working with the Roman rat lines/strains

Country/City/Main Investigator/s & Main findings (or research lines)	**Main references**
Birmingham, UK / Broadhurst, Fulker, Hewitt, Wilcock (i)- 1st diallel cross of 8 rat strains (RLA, RHA and RCA, MR and MNR, TMB and TMD, and WAG control strain), and a triple cross design including wild-type live-trapped rats***. First genetic evidence to support the notion that two main (genetically-driven) processes are involved in the TWAA task, an initial dominant tendency to freeze*** (i.e. due to Pavlovian conditioned fear), which runs against escaping/avoiding the unconditioned stimulus (i.e. electric shock-), and a ***tendency that comes to play a role later in the process of acquisition, which favors the appearance of active crossings*** (escapes/avoidances) to the opposite compartment	Fulker et al., 1972; Hewitt and Fulker 1983; Hewitt et al., 1981 Wilcock and Broadhurst 1967; Wilcock and Fulker 1973; Wilcock et al., 1981)
(ii)- Pioneers in showing that GABA production was related to two-way avoidance acquisition and exploratory activity in the open-field test, in studying the relationship between anxiety in a hyponeophagia test and brain levels of benzodiazepine receptors, and the ***genetic architecture of both hyponeophagia and the anxiolytic effects of diazepam in rats, using the RHA, RLA and RCA rat lines and 15 other rat crosses, as well as undertaking the first inter-rat line study on cholinergic transmission***	Buxton et al., 1976; Rick et al., 1971; Shephard et al., 1982, 1984, 1985
London, UK / Imada ***First demonstration that RLA rats are more sensitive to classical aversive conditioning than are RHA, MNR and MR rats***, i.e. the former showed the highest signs of fear-mediated (shock-induced) behavioral suppression of water drinking	Imada 1972

Supplementary Table 1 (continued)

<u>Thunder Bay, Canada / Satinder</u> (i)- Studies on the genetic-dependent and ontogenetic effects of amphetamine, ethanol, caffeine and morphine on emotionality and avoidance behavior, comparing the RLA/Lu, RHA/Lu, RCA/Lu with MNR/Har/Lu and MR/Har/Lu strains. Proposal of an ***U-inverted relationship between the degree of arousal and performance***	Satinder and Sterling 1983; Satinder and Wooldridge 1986 Satinder 1971, 1972, 1975, 1976b, 1981 Satinder 1977
(ii)-First demonstration**, *in ethological predator tests, that RLA rats were among the most anxious of those five groups of rats when subjected to the presence of a cat, a rabbit or an empty box***	Satinder 1976a
<u>Zürich, Basel, Lausanne and Geneva, Switzerland / Driscoll, Bättig, Steimer, Gentsch, Lipp; also in collaboration with Tucson, AZ, USA/ Overstreet, and Bagneux, France/ Scatton, Dedek</u> (i)- ***First comprehensive evidence that RLA rats are more anxious/fearful and*** **sensitive to stress *than RHA rats are***: The former ambulated (explored) less, defecated more and showed higher stress-induced corticosterone, ACTH and prolactin responses in open-field-like tests and novelty situations. RLA dams showed a more protective nursing behavior	Driscoll and Bättig 1979, 1982; Driscoll et al., 1979, 1991; Duetsch and Bättig 1977; Gentsch et al., 1981a, 1982, 1988, 1991
(ii)- First ***demonstration of cognitive impairment and impulsive traits in RHA, vs RLA, rats.*** RHA rats were less capable of learning a DRL20 operant task (which requires inhibition of irrelevant/impulsive behavior) and, related to this impulsive profile, they also showed reduced efficiency in non-spatial and spatial maze learning	Bättig and Schlatter 1978, 1979; Bättig et al., 1976; Nil and Bättig 1981; Schlatter and Bättig 1979, 1981; Zeier et al., 1978

Supplementary Table 1 (continued)

(iii)- Between-line differences in central serotoninergic, cholinergic, noradrenergic and dopaminergic systems, including studies on the differential effects of stressful environmental stimuli on mesocortical and mesoaccumbens dopaminergic neurons. Determination of differences in the density of brain imipramine, paroxetine and diazepam receptor binding sites, in line with findings that imipramine diazepam and pentobarbital differentially affected tunnel maze exploration and anxiety-related behavior in both rat lines	Charnay et al., 1995; D'Angio et al., 1988; Driscoll and Stübi, 1985; Driscoll et al., 1980, 1983, 1985, 1990, 1995; Gentsch et al.; 1981b, 1983; Martin et al., 1981, 1982; Overstreet 1995; Overstreet et al., 1981; Scatton et al., 1988
(iv) Differential responses to behavioral and ***stereotypic responses induced by amphetamine and apomorphine, as well as both a higher turnover rate of striatal dopamine and alcohol preference in RHA rats***	Driscoll 1986; Driscoll and Bättig, 1982; Driscoll et al., 1985, 1986, 1990 (see also Durcan et al., 1984, Brewster 1969, and Drewek and Broadhurst, 1979)
(v)- The ***size of hippocampal mossy fibers is negatively related to TWAA acquisition in the Roman rats and in mice***	Lipp et al., 1984, 1988, 1989
(vi)- ***Studies on differential coping styles of the RHA and RLA lines, as well as differential endocrine responses to stress*** and their ***neural modulation, and central dopaminergic mechanisms involved in the impulsivity profile and sensitivity to drugs of abuse in both lines***	Boersma et al., 2009; Coppens et al., 2012, 2013; Steimer and Driscoll 2003, 2005; Steimer et al., 1997a-b, 2007; Walker et al., 1989, 1992; Aubry et al., 1995; Charnay et al., 1995; Dimiziani et al., 2019; Tournier et al., 2013, 2018
Halifax, Canada / Henke First in reporting that a specific type of ***activity in the central amygdala is associated with emotional reactivity and increased stress-induced stomach pathology. This*** type of activity was only observed ***in RLA rats and in (other) Wistar rats*** selected for their high emotional profiles	Henke 1988a,b
Groningen, The Netherlands / Koolhaas	Meerlo et al., 1997; Roozendal et al., 1992, 1993; Wiersma et al., 1997, 1998

Supplementary Table 1 (continued)

(i)- Studies on the function of central amygdala (CeA), its modulation by CRF, vasopressin or oxytocin administration, and changes in behavioral (coping) and physiological (i.e. heart rate) stress- and fear-related responses: ***regulation of fear and stress responses by CeA was more important in the RLA rats***	
(ii)- ***Differential insulin resistance, metabolism and obesity in the Roman rat lines were measured,*** relating these processes with the rats' coping style and central dopaminergic function, and comparing them with the "proactive" and "passive", Wild-Type Groningen rats	Boersma et al., 2009, 2011a,b, 2012; Evers et al., 2017
Paris, France / Delacour, Guenaire (i)- Compared with their RLA and RCA rat lines, ***RHA rats were impaired in non-spatial working memory and spatial learning/memory***	Guenaire and Delacour, 1985; Guenaire et al., 1986; Willig et al., 1991a-b, 1992
(ii)- Intracerebroventricular administration of p-octopamine, a trace amine reported to reverse some stress- hormonal responses and the context-conditioned suppression of locomotor activity, improved TWAA acquisition in RLA rats to the level of untreated RHA rats. ***Hippocampal lesions also markedly improved TWAA acquisition in RLA rats***	Becú-Villalobos et al., 1992; Coulon et al., 1989; David and Delacour, 1980; David et al., 1982; Delacour et al., 1983; Delacour and Guenaire, 1983; Ennaceur et al., 1986; Guenaire and Delacour, 1983
Bordeaux, France / Mormede (i)- ***Characterization of immunological, behavioral and neuroendocrine stress-*** and **anxiety-related responses in Roman rats** derived from the Roman/Verh lines, and analysis of the genetic association among some of these traits, as well as in differences in the selection trait, i.e. two-way active avoidance behavior. Demonstration of ***a genetic association between TWAA acquisition and prolactin responses to stress***	Castanon and Mormede 1994; Castanon et al., 1992, 1994, 1995; Kulikov et al., 1995; Sandi et al., 1991
(ii)- RHA vs. RLA differences in preference for alcohol, saccharin, and quinine, as well as in sensitivity to cocaine effects: their modulation by sex and gonadal hormones	Haney et al., 1994; Razafimanalina et al., 1996

Supplementary Table 1 (continued)

Newark, DE, USA / Siegel ***RHA rats are sensation/novelty seeker rats*** and, similar to what had been observed in novelty seeker cats and humans, RHA rats (compared with RLA and Wistar control rats) ***are cortical-evoked-potential augmenters***	Siegel 1997; Siegel and Driscoll, 1996; Siegel et al., 1993, 1996 (see also Saxton et al., 1987a,b)
Warsaw, Poland / Pisula, Meyza (i)- Using novel testing procedures, RHA rats ***showed much more novelty seeking behavior*** than RLA rats did	Pisula 2003; Pisula and Osinski, 2000
(ii)- ***Medial prefrontal cortex, hippocampus, and basolateral/central amygdala were more active*** (measured by cFos expression) ***in RLA than RHA rats*** under stressful, spatial ***novelty/conflict*** conditions	Meyza et al., 2009
Mainz and Magdeburg, Germany / Schwegler, Yilmazer-Hanke, Seidel (i)-Studies of differences in the amygdala and associations with fear- and anxiety-related responses provides evidence that the ***amygdala of RLA rats is more functional than that of their RHA*** counterparts	Schwegler et al., 1997; Yilmazer-Hanke et al., 2002, 2016
(ii)- The ***pineals of RHA rats are twice as active in melatonin production than those of RLA rats***, and the pineal gland is also larger in RHA rats, also exhibiting an increased density of pineal synaptic ribbons	Seidel et al., 1990 (see also Requintina et al., 1994)
Cagliari, Italy / Giorgi, Corda, Quartu, Serra, Sanna	Corda et al., 1997, 2005, 2014; Fattore et al., 2009; Giorgi et al., 1994, 1997, 2005a-b, 2007, 2015; Lecca et al., 2004; Piras et al., 2003; Rosas et al., 2018

Supplementary Table 1 (continued)

(i)- ***First demonstration that RHA rats are more sensitive to the acute and chronic (i.e. sensitization) effects of drugs of abuse, are more vulnerable to drug addiction***, and have a ***more functional mesolimbic dopaminergic system***	
(ii)- ***RHA rats display higher sexual motivation and sexual activity than do RLA and SD rats.*** Sexual activity induces rat line-dependent neural activation in limbic brain areas involved in motivation and reward, leading to changes in synaptic plasticity (as measured by c-Fos, DFosB, BDNF, its receptor trkB, and Arc) with sexual experience acquisition, thus showing that these synaptic changes depend on the animals' genotype/phenotype	Sanna et al., 2013, 2014a,b; 2015, 2017, 2019 (see also Melis et al., 2019)
(iii)- ***Mesocortical dopamine release/function is dissociated from fear-related and coping behavior*** in a manner that is dependent upon the rat line, and the functional ***tone of the serotoninergic projection to the prefrontal cortex is stronger in RHA rats*** than in RLA rats	Giorgi et al., 2003a,b (see also Piras et al., 2010, 2014)
Barcelona, Spain / Fernández-Teruel, Tobeña, Morón, Torres; also in collaboration with: Oxford, UK/ Flint, Mott; Almería, Spain/ Flores, Moreno; Madrid, Spain/ Pellón; Bochum, Germany/ Anselme; Fort Worth, TX, USA/ Papini; Bristol, UK/ Lodge; (i)- First ***evidence that neonatal handling (NH), and/or juvenile-adult environmental enrichment lead to profound lifetime effects*** on many behavioral/cognitive and endocrine traits of the Roman rats, ***often eliminating the differences between them. NH significantly improves adult acquisition of two-way active avoidance in RLA rats***	Escorihuela et al., 1995a-b; Fernandez-Teruel et al., 1991, 1992a-b, 1993, 1994, 1997, 1998, 2002a,c; Ferré et al., 1994; Rio-Alamos et al., 2015, 2017b, 2019; Steimer et al., 1998
(ii)- ***First quantitative genetic study on multiple anxiety-related traits***, with > 800 F2 rats of both sexes (hybrids from the inbred RHA and RLA strains), revealing for the first time in rats the existence of pleiotropic QTL ("quantitative trait loci") influencing several conditioned and unconditioned anxiety- and fear-related traits.	Aguilar et al., 2002b, 2003; Escorihuela et al., 1999; Fernandez-Teruel et al., 2002b (see also Johannesson et al., 2009)

Supplementary Table 1 (continued)

First demonstration of genetic parent-of-origin effects on coping (anxiety-related) behavior in genetically heterogeneous (NIH-HS) and Roman rats	Mont et al., 2018
(iii)- Convincing evidence that, besides being anxious and passive coping animals, ***RLA rats display enhanced frustration responses to incentive loss in different paradigms,*** and might ***constitute a unique tool for research on the neurobiology of frustration***	Cuenya et al., 2012, 2015; Gomez et al., 2008, 2009a-c; Manzo et al., 2014a, 2015; Moron et al., 2010; Papini et al., 2015; Rosas et al., 2007; Sabariego et al., 2011, 2013; Torres and Sabariego 2014; Torres et al., 2005, 2007
(iv)- ***RHA*** (but not RLA) rats show a stop codon ***mutation at cysteine 407 in Grm2*** (cys407*; mGlu2 receptor), which allows the RHA strain to represent a ***naturally-occurring "knock out" of mGlu2*** receptors	Wood et al., 2017 (see also Fomsgaard et al., 2018; Klein et al., 2014)
(v)- As compared to RLA rats, ***RHA rats exhibit impulsivity*** in several tasks, ***impaired attentional/cognitive*** profiles and ***alterations of social behavior***, decreased volume and/or activity of the medial prefrontal cortex (PFC), hippocampus and amygdala, as well as a number of alterations of neurodevelopment-related pre-/postsynaptic markers and in the pyramidal spine density in the PFC, all of which indicate the presence of an ***immature PFC and a schizophrenia-like phenotypic profile*** in RHA rats	Merchan et al., 2019; Moreno et al., 2010; Del Río et al., 2014; Río-Álamos et al., 2017a, 2019; Tapias-Espinosa et al., 2019; Elfving et al., 2019; Fomsgaard et al., 2018; Klein et al., 2014; Sánchez-González et al., 2021; Sampedro-Viana et al., 2021

Supplementary Table 1 (continued)

LEGEND TO SUPPLEMENTARY TABLE 1.- Relevant endeavors/ findings/achievements from the different groups/laboratories are highlighted in bold italics. Abbreviations.- TWAA: two-way active avoidance. RLA, RHA and RCA: Roman Low-avoidance, Roman High-avoidance and Roman Control-Avoidance (derived from random mating of Wistar rats). RLA/Lu, RHA/Lu, RCA/Lu: these are the corresponding names of the three Roman lines established at Lakehead University (Thunder Bay, Canada) by Dr. P. Satinder (Satinder 1971). MR and MNR: Maudsley Reactive and Maudsley Non-Reactive (MNR/Har/Lu and MR/Har/Lu are the corresponding names of both Maudsley rat lines established at Lakehead University, Ontario, Canada, by Dr. P. Satinder (see Satinder 1971) . TMB and TMD: Tyron Maze Bright and Tyron Maze Dull (see Koene and Vosen 1991). WAG: Wistar Albino Glaxo control strain. Grm2, mGlu2 receptor: metabotropic glutamate 2 receptor.

Table S2

Supplementary Table 2 (S2). Effects of anxiolytic or anxiogenic drug treatments on anxiety-related behaviors in RLA and RHA rats

Drug	Dose (mg/kg)	Drug class	Effect on anxiety index/responses	References
ACUTE ANXIOLYTIC-LIKE DRUG TREATMENTS				
Diazepam	1.0	Anxiolytic BZ	Decrease of eating latency more marked in RLA rats (hyponeophagia anxiety test)	Shephard and Broadhurst, 1983
l-propranolol	6.0	Anxiolytic β-A-R antagonist	Decrease of eating latency more marked in RLA rats (hyponeophagia anxiety test)	Shephard and Broadhurst, 1983
Methysergide	6.0	Anxiolytic 5-HT-R antagonist	Decrease of eating latency more marked in RLA rats (hyponeophagia anxiety test)	Shephard and Broadhurst 1983
Pentobarbital	8.0, 16.0	Anxiolytic $GABA_A$-R chloride channel agonist	Increased avoidance behavior and decreased freezing response in two-way avoidance acquisition in RLA rats	Driscoll and Stübi, 1985
Chlordiazepoxide	2.5	Anxiolytic BZ	Increase of entries into the illuminated open-field-like center of the hexagonal tunnel maze in RLA rats	Martin et al., 1982
Flumazenil	5.0	Antagonist of BZR (with known anxiolytic-like effects at low doses)	Decrease of response failures (i.e. freezing responses) and increase of escape responses in two-way avoidance acquisition in RLA rats	Fernández-Teruel et al., 1991b
Diazepam	0.3, 1.0	Anxiolytic BZ	Decreased latency to the first crossing from the dark to the light compartment in the light/dark box anxiety test in RLA rats	Steimer and Driscoll, 2003
Diazepam	1.0	Anxiolytic BZ	Increased avoidance behavior in RLA rats in a conflict-like (anxiogenic) one-way active avoidance task (with only 1 s allowed in the safe side)	Torres et al., 2007
Diazepam	1.0, 2.5	Anxiolytic BZ	Increase in punished drinking in the Vogel's conflict test (similar magnitude in RLA and RHA rats)	Corda et al., 2018
p-Octopamine (*)	0.25 (i.c.v.)	Trace amine with anxiolytic-like effects In other tests	Increase in two-way active avoidance acquisition of RLA rats to the level of untreated (control) RHA rats	Delacour et al., 1983
Ethanol	0.25 (g/kg)	Pro-GABAergic with anxiolytic-like effects in other tests	Behavioral disinhibition in the hole-board test in RLA rats: marked increase of time spent head-dipping into the holes containing novel/unknown objects, without changes in locomotor activity.	Guitart-Masip et al., 2006a

Supplementary Table 2 (continued)				
PERINATAL OR CHRONIC ANXIOLYTIC-LIKE DRUG TREATMENTS				
Perinatal flumazenil	3.7	Antagonist of BZ-R (given from ED15 to PND 14))	Increased avoidance behavior and decrease of freezing responses in two-way avoidance acquisition in RLA rats	Escorihuela et al., 1995a
Perinatal flumazenil	3.5, 6.3	Antagonist of BZ-R (given from ED15 to PND 14)	Increased avoidance behavior and decrease of freezing responses in two-way avoidance acquisition in RLA rats	Ferré et al., 1996
Prenatal diazepam	1.0, 3.0	Anxiolytic BZ (ED 15 to ED 20)	Decrease of freezing responses and increase of escape responses in the two-way avoidance acquisition task in RLA rats	Driscoll et al., 1995
Repeated morphine	14.0, 224.4	μ-R, δ-R, and κ-R agonist (escalating doses, 5 days)	Increase of avoidance responses in the two-way avoidance acquisition task (1 h after last morphine injection) particularly in RLA rats	Satinder, 1976b
ACUTE ANXIOGENIC DRUG TREATMENTS (OR DRUG WITHDRAWAL-INDUCED ANXIOGENIC-LIKE EFFECT)				
5-MeODMT	2.5	Anxiogenic 5-HT-R agonist	Increase of eating latency in the hyponeophagia test, more markedly in RLA rats	Shephard and Broadhurst, 1983
PTZ	10.0, 15.0	Anxiogenic $GABA_A$ -R chloride channel blocker	Increase of self-grooming and freezing behavior (anxiety-related responses) in RLA rats. Similar to the effects of tail-pinch stress	Giorgi et al., 2003a
ZK93426	15.0	Anxiogenic β-carboline derivative, partial inverse agonist acting at BZ-Rs	Increase of freezing and tendency to increase self-grooming (anxiety-related responses) in RLA rats. Similar to the effects of tail-pinch stress	Giorgi et al., 2003a
PTZ	10.0, 15.0	Anxiogenic $GABA_A$ -R chloride channel blocker	More marked decrease of punished drinking responses in the Vogel's licking suppression conflict test in RLA than RHA rats	Corda et al., 2018
Withdrawal from repeated morphine	14.0, 224.4	μ-R, δ-R, and κ-R agonist (escalating doses, 5 days)	Decrease of avoidance responses in the two-way avoidance acquisition task (48 and 96 h after withdrawal)	Satinder, 1976b

(*) The trace amine p-octopamine has been reported to display anxiolytic-like effects, as it markedly reduced conditioned suppression of locomotor activity in rats (i.e. reverses the suppression of activity of rats exposed to a context associated, through Pavlovian conditioning, with footshocks 24 h before (Delacour and Guenaire, 1983), it improves two-way active avoidance acquisition in Sprague-Dawley rats without affecting, or even reducing, baseline locomotor activity (David et al., 1982). The concentrations of p-octopamine in the brain stem and hypothalamus are negatively associated with the levels of emotional stress (Ennaceur et al., 1986). Abbreviations: BZ, benzodiazepine; BZ-R, benzodiazepine receptor; β-A-R, beta-adrenergic receptor; $GABA_A$-R, γ-aminobutyric acid-A receptor; ED, embryonic day; PND, postnatal day; μ-R, δ-R, and κ-R, μ-, δ-, and κ- opioid receptors; PTZ, pentylenetetrazole.