Minireviews

Dopamine D₂ Receptor Supersensitivity as a Spectrum of Neurotoxicity and Status in Psychiatric Disorders

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ABSTRACT

Abnormality of dopamine D₂ receptor (D₂R) function, often observed as D₂R supersensitivity (D₂RSS), is a commonality of schizophrenia and related psychiatric disorders in humans. Moreover, virtually all psychotherapeutic agents for schizophrenia target D₂R in brain. Permanent D₂RSS as a feature of a new animal model of schizophrenia was first reported in 1991, and then behaviorally and biochemically characterized over the next 15–20 years. In this model of schizophrenia characterized by production of D₂RSS in ontogeny, there are demonstrated alterations of signaling processes, as well as functional links between the biologic template of the animal model and ability of pharmacotherapeutics to modulate or reverse biologic and behavioral modalities toward normality. Another such animal model, featuring knockout of trace amine-associated receptor

1 (TAAR1), demonstrates D₂RSS with an increase in the proportion of D₂R in the high-affinity state. Currently, TAAR1 agonists are being explored as a therapeutic option for schizophrenia. There is likewise an overlay of D₂RSS with substance use disorder. The aspect of adenosine A_{2A}-D₂ heteroreceptor complexes in substance use disorder is highlighted, and the association of adenosine A_{2A} receptor antagonists in discriminative and rewarding effects of psychostimulants is outlined. In summary, these new animal models of schizophrenia have face, construct, and predictive validity, and distinct advantages over earlier models. While the review summarizes elements of D₂RSS in schizophrenia per se, and its interplay with substance use disorder, a major focus is on presumed new molecular targets attending D₂RSS in schizophrenia and related clinical entities.

Introduction

While the phenomenon of dopamine (DA) D₂ receptor (D₂R) supersensitivity (D₂RSS) had long been implicated in a number of clinical states (schizophrenia and tardive dyskinesia, attention-deficit hyperactivity disorder, Tourette, Parkinson's disease, Huntington's chorea, reactivity to substances of abuse, and other neuropsychiatric disorders), the directed experimental focus on D₂RSS has been in vogue for only the past 30 years. This review highlights the production of D₂RSS and its seminal role in animal modeling of schizophrenia and substance abuse. The ability of pharmacological agents to alter molecular events and thereby reverse behavioral abnormalities in relevant animal models gives credence to the possibility of new treatments in humans directed toward ameliorating D₂RSS.

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ABBREVIATIONS: A_{2A}R, adenosine A_{2A} receptor; AMPH, amphetamine; DA, dopamine; D₁R, dopamine D₁ receptor; D₂R, dopamine D₂ receptor; D₂RSS, dopamine D₂ receptor supersensitivity; D₃R, dopamine D₃ receptor; EEDQ, 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline; KO, knockout; NAC, nucleus accumbens; NMDA, N-methyl-D-aspartate; PFC, prefrontal cortex; TAAR1, trace amine-associated receptor 1.

However, other receptor systems are also involved in schizophrenia and substance use disorder. Thus, multiple D₂ heteroreceptor complexes with receptor-receptor interactions exist in the ventral striatum and can modulate D₂RSS (Fuxe et al., 2014a,b; Borroto-Escuela et al., 2016a). They are of relevance for schizophrenia, and the presence of adenosine A_{2A} receptor (A_{2A}R)-D₂R, serotonin 5-hydroxytryptamine_{2A}-D₂R, NTS1-D₂R, and oxytocin R-D₂R heteroreceptor complexes has been demonstrated. Thus, neurotransmitters such as serotonin (5-hydroxytryptamine), neurotensin, and oxytocin, and the neuromodulator adenosine can modulate D₂RSS via their receptor protomers in D₂R heteroreceptor complexes.

Production of DA D₂RSS: Neurochemical and Behavioral Effects Relating to a Mimic of Schizophrenia Abnormalities

Perinatal repeated treatment of rats with the DA D₂R agonist quinpirole consistently results in the development of D₂RSS—a priming phenomenon, with D₂RSS persisting life-long (Kostrzewa and Brus 1991; Kostrzewa et al., 1993a,b, 2004, 2008; Kostrzewa, 1995). These primed rats, as adults, are virtually indistinguishable behaviorally from untreated rats, except if challenged with agents that impinge on the D₂R. A single challenge dose of quinpirole to primed rats initially produces short-lived enhancement of yawning (Kostrzewa and Brus, 1991; Kostrzewa et al., 1993a; Plech et al., 1995), an action known to be mediated by the dopamine D₃ receptor (D₃R) (Collins et al., 2005). In these primed rats quinpirole likewise induces oral activity (Kostrzewa et al., 1990), vertical jumping (between 3 and 5 weeks of age) (Kostrzewa et al., 1993b; Kostrzewa and Kostrzewa, 2012), altered antinociceptive response to a hot plate (Kostrzewa et al., 1991), and a variety of stereotypic actions (Kostrzewa et al., 1990; Brus et al., 2003). However, the B_{max} (i.e., number of D₂R) and K_d (affinity) values for striatal D₂R were unaltered in the primed rats (Kostrzewa and Brus, 1991). The general D₂R template and its interaction with a ligand has been illustrated (Männel et al., 2017) while its unique deep orthosteric binding pocket has been demonstrated at the molecular level (Wang et al., 2018). In rats displaying D₂RSS, active avoidance responding to quinpirole challenge was improved (Brus et al., 1998b) but there was a deficit in learning and memory tasks (Brus et al., 1998a; Brown et al., 2004a, 2005) and in the Whishaw skilled reaching task (Brown et al., 2002, 2004a). The deficits observed in learning and memory tasks were associated with a reduction in the expression of hippocampal nerve growth factor (Brown et al., 2004b) and was reversed by prolonged treatment with olanzapine, an atypical antipsychotic agent (Thacker et al., 2006).

Important to note is that quinpirole is a DA “D₂-like” agonist, in that it binds to DA D₂R subtypes D₂, D₃, and D₄ with significant affinity. It is known that the D₃R colocalizes with the dopamine D₁ receptor (D₁R) and forms D₁-D₃ receptor heteromers in neuronal populations in the dorsal striatum and nucleus accumbens (NAC) (Fiorentini et al., 2008; Marcellino et al., 2008). These heteromers may be involved in regulation of not only rewarding mechanisms, but also emotional and cognitive processes as well as motor function (Fiorentini et al., 2010). The DA D₁/D₃ heteromer in these brain areas may play a significant role in some of the

observed behavioral and neurobiological effects reported for quinpirole-primed rats.

For example, in adult rats that were quinpirole primed, an acute challenge dose of amphetamine (AMPH) is associated with a 5-fold increase in evoked DA release, as assessed by in vivo microdialysis in awake freely moving rats (Nowak et al., 2001). Enhanced AMPH-evoked release has been related to subsensitivity of D₂ autoreceptors (Seutin et al., 1991; Marinelli et al., 2003; Tammimäki et al., 2006), prompting the question of whether quinpirole priming, in part, may produce subsensitization of D₂ autoreceptors (Kostrzewa et al., 2016). The concept of quinpirole induction of subsensitivity of D₂ autoreceptors relates to the aforementioned results.

Quinpirole-primed rats displayed enhanced behavioral sensitization to AMPH in adulthood (Cope et al., 2010) and to nicotine in both adolescence (Perna and Brown, 2013) and adulthood (Perna et al., 2008). Furthermore, quinpirole-primed rats demonstrated enhanced DA release in the NAC core in response to both AMPH and nicotine (Perna and Brown, 2013).

Using in situ hybridization, RGS9, the transcript regulating G-protein coupling to the D₂R, was shown to be decreased in the NAC and frontal cortex of these primed rats (Maple et al., 2007). Moreover, rats with ontogenetically induced D₂RSS displayed deficits in prepulse inhibition when adult, analogous to prepulse inhibition deficits found in schizophrenics (Brown et al., 2012). Notably, D₂RSS and diminished RGS9 expression is also reported in the brain of schizophrenics (Seeman et al., 2007). Overall, the altered neurobiological template of brain deriving from D₂RSS is considered to be a reasonable modeling of schizophrenia (Brown et al., 2012; Maple et al., 2015; Kostrzewa et al., 2016).

Another important research area with quinpirole has been related to the behavioral and neurobiological responses to nicotine, based on past findings that reported a high rate of cigarette smoking in the population diagnosed with schizophrenia (Winterer, 2010). In quinpirole-primed rats, alpha-7 nicotinic receptor binding was increased in striatum and hippocampus, and the enhanced behavioral effects of an acute challenge dose of quinpirole were reduced by nicotine (Perna et al., 2008).

The latter action of nicotine was blocked by the nicotinic receptor antagonist mecamylamine (Tizabi et al., 1999). In addition, rats that were neonatally quinpirole-primed have shown increased behavioral sensitization to nicotine (Sheppard et al., 2009; Perna and Brown, 2013), conditioned place preference to nicotine (Brown et al., 2018), and enhanced DA (Perna and Brown, 2013) and brain-derived neurotrophic factor responses to nicotine (Peterson et al., 2017) in the NAC, a brain area that mediates drug reward. All these findings are consistent with the hypothesis that a D₂RSS system is enhanced in its sensitivity to the rewarding aspects of nicotine. Furthermore, prolonged nicotine treatment of quinpirole primed rats reduced the learning deficit (Morris water maze) and skilled reaching deficit; and reversed the reduction in hippocampal nerve growth factor and brain-derived neurotrophic factor produced by neonatal quinpirole treatment (Brown et al., 2006, 2012). Interestingly, these data are consistent with the hypothesis that nicotine may be used as self-medication toward cognitive impairments known to exist in schizophrenia (Leonard et al., 2007).

In related studies on DA D₃R, neither quinpirole (D₂R, relatively selective) nor (+/-)-2-(dipropylamine)-7-hydroxy-1,2,3,4-tetrahydronaphthalene (D₃R selective) were able to prime D₃R (Oswiecimska et al., 2000), thus indicating that the priming process is mostly associated with D₂RSS.

The D₁-D₃ heteroreceptor complexes exist in the direct pathway, especially after degeneration of nigro-striatal dopaminergic neurons, and in the reward neurons of the NAC (Fiorentini et al., 2008; Marcellino et al., 2008); D₃R agonist activity of quinpirole is well-established. It should therefore be considered that the D₁R also can participate in the aforementioned studies. The D₃Rs are known to enhance the actions of D₁R. The enhancement of D₁R protomer signaling by D₃ protomer activation may also play a significant role.

Production of DA D₂RSS: Neurochemical and Behavioral Effects Relating to a Mimic of Parkinson's Disease Abnormalities

Quinpirole-induced striatal D₂RSS was demonstrated in the hemiparkinsonian rat model based on induction of contralateral turning behavior and enhanced inhibition of neuronal firing rates in this brain area (Strömberg et al., 2000). The mechanism related to the previous finding is linked to an enhanced coupling of postjunctional D₂-like receptor to G proteins via (inter alia) reduction in G protein-coupled receptor kinase activity (Gainetdinov et al., 2003). D₂RSS may also develop as a result of enhanced inhibition of protein kinase tyrosine/mitogen-activated protein kinase phosphatase activity (Zhen et al., 2002). Furthermore, D₂RSS-like development is also associated with calcium current modulation which participates in regulation of the excitability of striatal efferent neurons (Prieto et al., 2009). In recent years it has been suggested that a reorganization of multiple D₂ heteroreceptor complexes in balance with each other can contribute to the development of D₂RSS (Fuxe et al., 2014a; Borroto-Escuela et al., 2016a). Taken together, all of the aforementioned mechanisms may be in operation in the dorsal and ventral striatum and have relevance for motor and reward/emotional functions, respectively, which can be disturbed both in Parkinson's disease and schizophrenia.

Developmental Differences in DA D₂^{High} Receptors

Dopaminergic dysfunction is a central component of many psychiatric illnesses that affects adult populations. As a natural outgrowth of this understanding, the pharmacological targeting of dopaminergic transmission is also a common strategy for treating pediatric age groups (Wall et al., 2012). This approach can be problematic since the efficacy of many of these drugs is based on adult responsiveness and may not be predictive of their effectiveness in developing organisms (Stephenson, 2005). In the preclinical literature, it is not uncommon for dopaminergic agonists and antagonists to have pronounced ontogenetic effects (Spear, 2000). Quantitative age-dependent behavioral differences are most frequently observed, since developing animals often display adult-typical responses that vary only in magnitude (McDougall et al., 2015). Occasionally, ontogenetic differences in drug responsivity can also differ in a qualitative manner, since

dopaminergic drugs may either leave a particular age group unaffected or induce distinctly different behavioral patterns across ontogeny (Moody and Spear, 1992).

One striking example of this type of developmental difference is the behavioral response to the irreversible DA receptor antagonist 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ). In adult rats, EEDQ reduces spontaneous behaviors and causes a dose-dependent reduction in DA agonist-induced locomotor activity. In sharp contrast, administering EEDQ to preweanling rats both increases basal locomotion and potentiates the effects of DA agonists (Der-Ghazarian et al., 2012, 2014). The cause of these age-dependent behavioral differences is uncertain; however, the potentiation effect is mediated by D₂R because only drugs that directly or indirectly stimulate D₂R (quinpirole and cocaine) produce an exaggerated locomotor response in EEDQ-treated preweanling rats (Der-Ghazarian et al., 2012, 2014). Receptor selectivity can also be established by pretreating rats with a reversible DA-R antagonist, such as raclopride or sulpiride, to protect D₂R from EEDQ-induced inactivation. In this case, protecting D₂R from the alkylating effects of EEDQ eliminated DA agonist-induced locomotor potentiation (Der-Ghazarian et al., 2012, 2014); thereby demonstrating that D₂R is the critical receptor type underlying the potentiation phenomenon.

Ontogenetic differences in the sensitivity of the D₂R may be at least partially responsible for the EEDQ-induced potentiation effect observed in young rats. Specifically, EEDQ (7.5 mg/kg) reduced D₂R densities in rats of various ages; however, the surviving D₂Rs of preweanling rats were preferentially in a high-affinity state (McDougall et al., 2014). GTP γ S binding, which is a measure of the functional relationship between G-proteins and the D₂R, was also significantly enhanced in the dorsal striata of EEDQ-treated preweanling rats relative to adult rats. Both sets of findings suggest that EEDQ causes D₂RSS in preweanling rats—an action that may be responsible for potentiating basal and DA agonist-induced locomotor activity.

D₂RSS may also be responsible for some of the quantitative differences in drug responsivity that are apparent across ontogeny. An older literature suggests that neonatal and preweanling rats, relative to adults, are more sensitive to the activation effects of DA agonists (Spear, 1979). Specifically, there is a leftward shift in the dose-response curve for DA agonists, with young rats showing maximal amounts of locomotor activity at lower doses than adolescent or adult rats (McDougall et al., 2015). We hypothesized that these age-dependent behavioral effects are due to a relative excess of high-affinity D₂R during early ontogeny. Consistent with this explanation, non-EEDQ-treated preweanling rats have a significantly greater percentage of dorsal striatal D₂^{High} receptors than adolescent or adult rats (McDougall et al., 2015).

In summary, there is accumulating evidence that behavioral responsiveness to dopaminergic drugs varies dramatically across ontogeny, and that age-dependent changes in the percentage of D₂^{High} receptors may be responsible for these behavioral differences. It is well established that D₂RSS is correlated with a number of neuropsychiatric conditions present in adulthood. Likewise, it is possible that D₂RSS may contribute to some of the DA-linked disorders first expressed during childhood and early adolescence (e.g., Tourette, attention-deficit hyperactivity disorder, etc.). More generally, the response characteristics of adults treated with

dopaminergic drugs may not always be predictive of pediatric responsiveness.

D₂RSS in Mice Lacking Trace Amine-Associated Receptor 1

The discovery of a new family of monoaminergic G-protein-coupled receptors, named trace amine-associated receptors (six functional receptors are found in humans), has significantly added to the understanding of the complexity of monoaminergic neurotransmission (Borowsky et al., 2001; Bunzow et al., 2001). The best investigated receptor, trace amine-associated receptor 1 (TAAR1), senses trace amines β -phenylethylamine, tyramine, tryptamine, octopamine, DA metabolite 3-methoxytyramine, and thyroid derivative 3-iodothyronamine, and some other biogenic amines that are found at low levels in mammalian brain (Grandy, 2007; Berry et al., 2017). TAAR1 is coupled to *Gas* heterotrimeric G-protein to stimulate the production of cAMP (Borowsky et al., 2001; Bunzow et al., 2001; Barak et al., 2008). In addition to the aforementioned trace amines, TAAR1 also senses other compounds such as adrenergic drugs, ergolines, apomorphine, octopamine, and psychostimulant drugs AMPH and methylenedioxymethamphetamine (Borowsky et al., 2001; Bunzow et al., 2001; Berry et al., 2017). In the brain, TAAR1 mRNA is found within primary monoaminergic areas such as the ventral tegmental area, substantia nigra, amygdala, frontal cortex, dorsal raphe, and striatum/NAC (Lindemann et al., 2008; Di Cara et al., 2011; Berry et al., 2017). Electrophysiological experiments performed on mouse brain slices also show that TAAR1 is functionally active in the ventral tegmental area and dorsal raphe (Bradaia et al., 2009; Revel et al., 2011). Altogether, these studies clearly demonstrate that TAAR1 is expressed and functional in brain monoaminergic systems and may therefore be implicated in the modulation of DA and 5-hydroxytryptamine neurotransmission.

Indeed, the first investigation of mice lacking TAAR1 revealed that these mutants demonstrate enhanced locomotor and neurochemical responses to psychostimulants and have an increased proportion of striatal D₂Rs in the high-affinity state (Wolinsky et al., 2007). These findings were corroborated by other groups that also reported psychostimulant supersensitivity in independently developed strains of TAAR1 knockout (KO) mice (Lindemann et al., 2008; Di Cara et al., 2011). Functional and physical interactions between D₂R and TAAR1 have been shown in a number of studies performed both in vitro and in vivo. Cellular mechanistic studies have revealed that D₂R long receptor (postsynaptic isoform) and TAAR1 form heteromers in human embryonic kidney cells and that application of DA receptor antagonists results in enhanced TAAR1 signaling (Espinoza et al., 2011; Harmeyer et al., 2015). Importantly, TAAR1-KO mice have reduced D₂R antagonist haloperidol-induced striatal c-fos expression and a reduction in haloperidol-induced catalepsy (Espinoza et al., 2011).

At the same time, both partial and full TAAR1 agonists neither cause catalepsy per se nor enhance haloperidol-induced catalepsy, but in fact somewhat reduce catalepsy (Revel et al., 2013). Further confirmation of interaction between striatal postsynaptic D₂R and TAAR1 is evidenced by the fact that D₂Rs, but not DA D₁Rs, are overexpressed and locomotor responses to D₂R, but not D₁R, agonists are enhanced in TAAR1-KO mice. An allosteric antagonistic

TAAR1-D₂R interaction in this receptor complex may contribute to these behavioral findings, implicating TAAR1 receptor antagonists as novel antiparkinsonian drugs. Further validation of interactions between striatal postsynaptic D₂R and TAAR1 is evidenced by the fact that D₂Rs, but not D₁Rs, are overexpressed and locomotor responses to D₂R, but not D₁R, agonists are enhanced in TAAR1-KO mice. These results indicate that TAAR1 also can exert an inhibitory transcriptional modulation of the D₂R.

Similarly, the profile of striatal postsynaptic signaling events in KO animals is altered only for D₂Rs with selectively activated D₂R-mediated G-protein-independent beta-arrestin 2-mediated AKT/GSK3 signaling pathways (Espinoza et al., 2015a). Coimmunoprecipitation studies directly demonstrate physical interaction of the two receptors in vivo in brain, resulting in altered subcellular localization of TAAR1 and an increase in D₂R agonist binding affinity (Liu and Li, 2018; Rutigliano et al., 2018). Also, activation of the TAAR1-D₂R heteroreceptor complex in cells negatively modulates beta-arrestin 2-mediated AKT/GSK3 β signaling (Harmeyer et al., 2015).

An altered presynaptic D₂R autoreceptor sensitivity is also found in TAAR1-KO mice. Electrophysiological investigations on brain slices have revealed that the lack of TAAR1 causes an increased firing rate of DA neurons in the ventral tegmental area and increased D₂R agonist potency (Bradaia et al., 2009). Furthermore, voltammetric and microdialysis studies in TAAR1-KO mice, and with use of selective TAAR1 ligands, have shown that TAAR1 regulates DA release, primarily in the NAC via interaction with presynaptic D₂ autoreceptors (Leo et al., 2014). This may involve the existence of TAAR1-D₂R autoreceptor complexes in the mesolimbic DA reward neurons. The removal of the TAAR1 protomer may lead to dysfunction of the D₂R protomer autoreceptor due to altered allosteric receptor-receptor interactions involving recruitment of other receptor protomers and proteins to the D₂ autoreceptor. In view of such events knockout of TAAR1 can give different results from those obtained with TAAR1 antagonists.

Given the evidence that mice overexpressing striatal D₂Rs have alterations in glutamatergic transmission in the prefrontal cortex (PFC) (Kellendonk et al., 2006), it is intriguing that TAAR1 can modulate PFC processes as well (Espinoza et al., 2015b). In fact, in the PFC layer V pyramidal neurons where TAAR1 is normally expressed, TAAR1-KO mice demonstrate a functional deficit of *N*-methyl-D-aspartate (NMDA)-mediated current and an altered subunit composition of the NMDA receptor. These data indicate that TAAR1 has a major modulatory role for cortical NMDA receptor-mediated glutamate transmission attending cognition (Espinoza et al., 2015b).

Finally, several recently identified selective TAAR1 agonists have been shown to effectively counteract hyperactivity induced by dopaminergic psychostimulants or NMDA receptor antagonists, and improved performance in schizophrenia-related cognitive tasks in rodents, indicating that TAAR1 agonists may represent a new class of drugs for the treatment of schizophrenia (Revel et al., 2011, 2012, 2013). Additionally, TAAR1 agonists are effective in preventing addictive behaviors in various rodent models. This may involve, at least in part, modulation of presynaptic D₂R autoreceptor-mediated control of DA release (Leo et al., 2014; Asif-Malik et al., 2017), and it suggests the potential utility of TAAR1 agonists in addiction (Pei et al., 2016). TAAR1 agonists likely also act at

postjunctional receptor complexes in the NAC and reduce the rewarding actions of substances of abuse (Liu and Li, 2018). This action may involve the formation of TAAR1-D₂R heteroreceptor complexes in the postjunctional plasma membrane with antagonistic allosteric receptor-receptor interactions (Espinoza et al., 2011; Harmeyer et al., 2015) reducing postjunctional D₂R protomer signaling in the ventral striato-pallidal GABA antireward neurons. TAAR1 agonists acting at these postjunctional TAAR-D₂ heteroreceptor complexes may, therefore, become novel compounds for treatment of substance use disorder.

Instead, if the TAAR1 agonist used preferentially acts at TAAR1-D₂ autoreceptor complexes, likely having a different stoichiometry and composition, altered allosteric receptor-receptor interactions can be obtained in the mesolimbic DA neurons. As a result, enhanced DA release in the mesolimbic DA reward neurons can develop. This can enhance the development of drug use disorder by impairing D₂ protomer autoreceptor function. This is an important area for further research in order to understand the true mechanisms involved. The complexity is increased through the existence of both pre- and postjunctional TAAR1 homo- and heteroreceptor complexes linked to mesolimbic DA neurons. This topic relating D₂R with substance abuse is discussed in greater detail subsequently.

A_{2A}-D₂ Heteroreceptor Complexes Associated with Substance Use Disorder: Psychostimulant and Antagonist Interplay

Substance use disorder (drug addiction) is defined as a chronic relapsing brain disorder, characterized by compulsive drug seeking and use despite destructive consequences. Substances of abuse induce a wide range of behavioral effects including pleasure and euphoria, which are related to increased DA neurotransmission in the brain reward system, including ventral striatum (i.e., NAC) and PFC. Among DA receptors, D₂Rs have been the most widely studied target for treatment of drug addiction. The D₂R is recognized as a hub receptor that forms heteromers with multiple receptors (e.g., the adenosine A_{2A}R) (Fuxe et al., 2008; Borroto-Escuela et al., 2016b). The antagonistic A_{2A}R-D₂R interaction in this heteroreceptor complex appears to be a major mechanism for the ability of A_{2A}R to counteract the inhibitory role of D₂R on neuronal excitability and neurotransmitter release, especially in NAC GABA and enkephalin-expressing neurons mediating antireward. These are modulated by antagonistic A_{2A}R-D₂R interactions taking place in heteroreceptor complexes located especially at the dendritic level (Fuxe et al., 2005). These actions within the A_{2A}R-D₂R heterocomplexes were demonstrated using biochemical binding techniques (Pintsuk et al., 2016) and in situ proximity ligation assay (Trifilieff et al., 2011; Borroto-Escuela et al., 2013) as well as in vivo studies (Filip et al., 2012).

The antagonistic A_{2A}R-D₂R interactions are also evident in cocaine reward and reinforcement as well as drug-seeking behavior. Thus, the A_{2A}R agonist 2-*p*-(2-carboxyethyl)-phenethylamino-5'-*N*-ethylcarboxamidoadenosine decreases, while the A_{2A}R antagonists (E)-1,3-diethyl-8-(3,4-dimethoxyphenylethyl)-7-methyl-3,7-dihydro-1*H*-purine-2,6-dione (acting mainly postsynaptically) and 5-amino-7-(β-phenylethyl)-2-(8-

furyl)pyrazolo(4,3-*e*)-1,2,4-triazolo(1,5-*c*)pyrimidine (mixed pre- and postsynaptic receptor antagonist) do not alter cocaine self-administration in rats (Wydra et al., 2015a). There are indications that they exert their behavioral actions mainly through targeting the A_{2A}R protomer of the A_{2A}R-D₂R heterocomplexes of the ventral striato-pallidal GABA pathway mainly originating in the NAC. Thus, observations exist that indicate disruption of these heteroreceptor complexes by A_{2A}R transmembrane 5 peptide administration leads to enhancement of cocaine self-administration (Borroto-Escuela et al., 2018).

A_{2A}R-KO mice display a lower rate of cocaine self-administration with a reduction in the maximal effort to obtain a cocaine infusion (Soria et al., 2006). The mechanism underlying attenuated reward behavior of A_{2A}R-KO mice is not clear but can be related to reorganization of the balance between multiple receptor complexes in which brain A_{2A}R are involved. Specifically, A_{2A}R agonists inhibit, while A_{2A}R antagonists potentiate, the motor, discriminative, and rewarding effects of psychostimulants (Filip et al., 2012). While A_{2A}R neuronal inactivation attenuates acute psychostimulant effects as well as psychostimulant behavioral sensitization, selective inactivation of striatal A_{2A}R enhances a psychostimulant effect and A_{2A}R inactivation in forebrain (including striatal, cortical, and hippocampal A_{2A}R) attenuates psychostimulant effects (Filip et al., 2012). These findings indicate that striatal and extra-striatal A_{2A}R have opposite modulatory effects on substances of abuse. The explanation may be the existence of facilitatory allosteric A_{2A}R-D₂R interactions in the heteroreceptor complexes of the cerebral cortex related to a dominance of D₂ beta-arrestin-2 signaling (Urs et al., 2016), which is favored by the A_{2A} protomer activation (Borroto-Escuela et al., 2011; Fuxe and Borroto-Escuela, 2016). The findings indicate the existence of an A_{2A}R-D₂R-beta-arrestin-2 heterocomplex which is favored by the antagonistic A_{2A}R-D₂R interaction (Borroto-Escuela et al., 2011). The A_{2A}R agonist favors an enhanced recruitment of beta-arrestin-2 to the D₂R protomer upon D₂R agonist cotreatment. This leads to cointernalization linked to a reduced time onset of AKT phosphorylation associated with a rapid dephosphorylation. In this way, beta-arrestin-2 resembles G-protein receptor signaling by becoming faster and having short duration.

It is of high interest that the D₂R structure uses a deep binding pocket to bind the atypical antipsychotic drug risperidone (Wang et al., 2018). Instead, D₃ and D₄ receptors bind substituted benzamides with the D₃ or D₄ receptor selectivity in another way via distinctly extended binding sites (Chien et al., 2010; Wang et al., 2017). This opens up new possibilities to develop novel, specific D₂R antagonists for treatment of schizophrenia and cocaine use disorder, with expected fewer adverse effects. It should also be considered that distinct homoreceptor and heteroreceptor complexes can be pathologically altered in the brain circuits involved in schizophrenia and cocaine use disorder versus other circuits (Borroto-Escuela et al., 2017b). Specifically targeting the vulnerable heteroreceptor complexes and restoring their balance in these circuits may also offer novel treatments with fewer adverse effects.

Cocaine self-administration was recently found to selectively increase the antagonistic A_{2A}R-D₂R interactions in ventral striatum in [³H]raclopride/quinpirole competition experiments (Pintsuk et al., 2016). An A_{2A}R agonist ex vivo reduced the affinity of the D₂R agonist high-affinity site after cocaine self-administration versus the effects in yoked saline

rats—effects not observed in dorsal striatum. Furthermore, cocaine self-administration specifically increased the A_{2A}R-D₂R and D₂R-sigma1 receptor heterocomplexes in the NAC shell (Borrito-Escuela et al., 2017a). Thus, cocaine self-administration appears to reorganize the A_{2A}R-D₂R heterocomplexes in this region, involving an increased presence of sigma1 receptors in these complexes. An increased density of such complexes is observed with enhancement of their antagonistic receptor-receptor interactions. These complexes in the NAC shell may, therefore, be the target of the anti-cocaine actions of A_{2A}R agonists.

The role of tonic activation of A_{2A}R in cocaine behaviors is reported for reinstatement of cocaine-seeking behavior (Wydra et al., 2015b). In this model the A_{2A}R antagonists reinstated cocaine- and cue-induced seeking, while the A_{2A}R agonist 2-*p*-(2-carboxyethyl)phenethylamino-5'-*N*-ethylcarboxamidoadenosine evoked a dose-dependent decrease of cocaine- and cue-induced seeking behavior in rats. Also, 2-*p*-(2-carboxyethyl)phenethylamino-5'-*N*-ethylcarboxamidoadenosine reduced D₂-like receptor agonist quinpirole-induced (the D₂-like receptor agonist) seeking behavior. Similar inhibitory effects on quinpirole-, cocaine-, cue- and A_{2A}R antagonist-induced seeking behavior were observed after treatment with the D₂-like receptor antagonist raclopride, indicating that A_{2A}R-D₂R heterocomplexes are also involved in cocaine seeking. Observed behavioral effects are in line with findings by other groups (Bachtell and Self, 2009; O'Neill et al., 2012).

Current studies support a role for A_{2A}R-D₂R heterocomplexes in the NAC in antagonizing cocaine reward, and reinstatement and A_{2A}R agonism may have therapeutic potential for preventing cue-controlled craving and relapse.

Summary and Conclusions

D₂RSS is a phenomenon associated with an array of human clinical and/or psychiatric states, 1) being produced by repeated agonist action at D₂R, which 2) promotes multiple reorganizations of the receptor-forming heteromers with adenosine, TAAR1, or other receptor types, 3) alters effects of D₂R activation on G-protein-dependent and -independent events, and 4) causes downstream alteration of receptor transduction/signaling—any of which produces an abnormality of behavior (or thought). D₂RSS has particular relevance to human disorders of thought (e.g., schizophrenia), behaviors (e.g., attention-deficit hyperactivity disorder), and neurodegenerative disorders (e.g., Parkinson's disease and Huntington's chorea). With insight having been gained on the process of D₂RSS, it is now conceivable that D₂RSS may represent a relevant target toward reversing abnormalities of a variety of human neural-associated disorders.

Authorship Contributions

Wrote or contributed to the writing of the manuscript: Kostrzewa, Wydra, Filip, Crawford, McDougall, Brown, Borrito-Escuela, Fuxe, Gainetdinov.

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