1521-0103/366/3/519–526$35.00
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS

https://doi.org/10.1124/jpet.118.247981
J Pharmacol Exp Ther 366:519–526, September 2018

The Journal of PHARMACOLOGY And Experimental Therapeutics

Minireviews

Dopamine D_2 Receptor Supersensitivity as a Spectrum of Neurotoxicity and Status in Psychiatric Disorders

Richard M. Kostrzewa, Karolina Wydra, Malgorzata Filip, Cynthia A. Crawford, Sanders A. McDougall, Russell W. Brown, Dasiel O. Borroto-Escuela, Kjell Fuxe, and Raul R. Gainetdinov

Department of Biomedical Sciences, Quillen College of Medicine, East Tennessee State University, Johnson City, Tennessee (R.M.K., R.W.B.); Institute of Pharmacology, Polish Academy of Sciences, Department of Drug Addiction Pharmacology, Krakow, Poland (K.W., M.F.); Department of Psychology, California State University, San Bernardino, California (C.A.C., S.A.M.); Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden (D.O.B.-E., K.F.); Institute of Translational Biomedicine, St. Petersburg State University, St. Petersburg, Russia (R.R.G.); and Skolkovo Institute of Science and Technology, Skolkovo, Moscow, Russia (R.R.G.)

Received January 22, 2018; accepted May 23, 2018

ABSTRACT

Abnormality of dopamine D_2 receptor (D_2R) function, often observed as D_2R supersensitivity (D_2RSS), is a commonality of schizophrenia and related psychiatric disorders in humans. Moreover, virtually all psychotherapeutic agents for schizophrenia target D_2R in brain. Permanent D_2RSS 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 D_2RSS 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 D_2RSS with an increase in the proportion of D_2R in the high-affinity state. Currently, TAAR1 agonists are being explored as a therapeutic option for schizophrenia. There is likewise an overlay of D_2RSS with substance use disorder. The aspect of adenosine A_{2A}-D_2 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 D_2RSS in schizophrenia per se, and its interplay with substance use disorder, a major focus is on presumed new molecular targets attending D_2RSS in schizophrenia and related clinical entities.

Introduction

While the phenomenon of dopamine (DA) D_2 receptor (D_2R) supersensitivity (D_2RSS) 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 D_2RSS has been in vogue for only the past 30 years. This review highlights the production of D_2RSS 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 D_2RSS.

Research funding for this work was provided by the Russian Science Foundation [Grant 14-50-00069] (to R.R.G.); the National Institutes of Health Division of Mental Health [Grant MH102930] (to S.A.M.); the National Institutes of Health National Institute of Neurological Disorders and Stroke [Grants NS29505 and NS39272] (to R.M.K.) and the John E. Fogarty International Center (to R.M.K.); statutory funds from the Institute of Pharmacology, Polish Academy of Sciences (to M.F. and K.W.); the Swedish Medical Research Council [Grant 62X-00715-50-3] (to K.F.); and the National Institutes of Health [Grant 1R15DA034912-A1] (to R.W.B.).

This work stems from a symposium on "Dopamine D_2 Receptor Supersensitivity as a Spectrum of Neurotoxicity and Status in Psychiatric Disorders," organized by R.M.K. and held during the Federation of European Neuroscience meeting in Pecs, Hungary, 2017 Sep 20–23, 2017. Portions of the material contained in this paper were presented at the symposium by C.A.C., R.R.G., K.W., and R.M.K.

https://doi.org/10.1124/jpet.118.247981.

ABBREVIATIONS: $A_{2A}R$, adenosine A_{2A} receptor; AMPH, amphetamine; DA, dopamine; D_1R, dopamine D_1 receptor; D_2R, dopamine D_2 receptor; D_2RSS, dopamine D_2 receptor supersensitivity; D_3R, dopamine D_3 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 D_2 heteroreceptor complexes with receptor-receptor interactions exist in the ventral striatum and can modulate D_2RSS (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)-D_2R, serotonin 5-hydroxytryptamine$_{2A}$-D_2R, NTS1-D_2R, and oxytocin R-D_2R heteroreceptor complexes has been demonstrated. Thus, neurotransmitters such as serotonin (5-hydroxytryptamine), neurotensin, and oxytoxin, and the neuromodulator adenosine can modulate D_2RSS via their receptor protomers in D_2R heteroreceptor complexes.

Production of DA D_2RSS: Neurochemical and Behavioral Effects Relating to a Mimic of Schizophrenia Abnormalities

Perinatal repeated treatment of rats with the DA D_2R agonist quinpirole consistently results in the development of D_2RSS—a priming phenomenon, with D_2RSS persisting lifelong (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 D_2R. 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 D_3 receptor (D_3R) (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 D_2R) and K_d (affinity) values for striatal D_2R were unaltered in the primed rats (Kostrzewa and Brus, 1991). The general D_2R 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 D_2RSS, 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 "D_2-like" agonist, in that it binds to DA D_2R subtypes D_2, D_3, and D_4 with significant affinity. It is known that the D_3R colocalizes with the dopamine D_1 receptor (D_1R) and forms D_1–D_3 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 D_1/D_3 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 D_2 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 D_2 autoreceptors (Kostrzewa et al., 2016). The concept of quinpirole induction of subsensitivity of D_2 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 D_2R, was shown to be decreased in the NAC and frontal cortex of these primed rats (Maple et al., 2007). Moreover, rats with ontogenetically induced D_2RSS displayed deficits in prepulse inhibition when adult, analogous to prepulse inhibition deficits found in schizophrenics (Brown et al., 2012). Notably, D_2RSS 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 D_2RSS 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 D_2RSS 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 D_3R, neither quinpirole (D_2R, relatively selective) nor (+/−)-2-(dipropylamine)-7-hydroxy-1,2,3,4-tetrahydronaphthalene (D_3R selective) were able to prime D_3R (Oswiecimska et al., 2000), thus indicating that the priming process is mostly associated with D_2RSS.

The D_1–D_3 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); D_3R agonist activity of quinpirole is well-established. It should therefore be considered that the D_1R also can participate in the aforementioned studies. The D_3Rs are known to enhance the actions of D_1R. The enhancement of D_1R protomer signaling by D_3 protomer activation may also play a significant role.

Production of DA D_2RSS: Neurochemical and Behavioral Effects Relating to a Mimic of Parkinson's Disease Abnormalities

Quinpirole-induced striatal D_2RSS 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 D_2-like receptor to G proteins via (inter alia) reduction in G protein-coupled receptor kinase activity (Gainetdinov et al., 2003). D_2RSS may also develop as a result of enhanced inhibition of protein kinase tyrosine/mitogen-activated protein kinase phosphatase activity (Zhen et al., 2002). Furthermore, D_2RSS-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 D_2 heteroreceptor complexes in balance with each other can contribute to the development of D_2RSS (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 D_2^{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 D_2R because only drugs that directly or indirectly stimulate D_2R (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 D_2R from EEDQ-induced inactivation. In this case, protecting D_2R from the alkylating effects of EEDQ eliminated DA agonist-induced locomotor potentiation (Der-Ghazarian et al., 2012, 2014); thereby demonstrating that D_2R is the critical receptor type underlying the potentiation phenomenon.

Ontogenetic differences in the sensitivity of the D_2R may be at least partially responsible for the EEDQ-induced potentiation effect observed in young rats. Specifically, EEDQ (7.5 mg/kg) reduced D_2R densities in rats of various ages; however, the surviving D_2Rs of preweanling rats were preferentially in a high-affinity state (McDougall et al., 2014). GTPγS binding, which is a measure of the functional relationship between G-proteins and the D_2R, 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 D_2RSS in preweanling rats—an action that may be responsible for potentiating basal and DA agonist-induced locomotor activity.

D_2RSS 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 activational 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 D_2R during early ontogeny. Consistent with this explanation, non-EEDQ-treated preweanling rats have a significantly greater percentage of dorsal striatal D_2^{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 D_2^{High} receptors may be responsible for these behavioral differences. It is well established that D_2RSS is correlated with a number of neuropsychiatric conditions present in adulthood. Likewise, it is possible that D_2RSS 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.

D_2RSS 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 Gαs 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 D_2Rs 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 D_2R and TAAR1 have been shown in a number of studies performed both in vitro and in vivo. Cellular mechanistic studies have revealed that D_2R 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; Harmeier et al., 2015). Importantly, TAAR1-KO mice have reduced D_2R 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 D_2R and TAAR1 is evidenced by the fact that D_2Rs, but not DA D_1Rs, are overexpressed and locomotor responses to D_2R, but not D_1R, agonists are enhanced in TAAR1-KO mice. An allosteric antagonistic TAAR1-D_2R 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 D_2R and TAAR1 is evidenced by the fact that D_2Rs, but not D_1Rs, are overexpressed and locomotor responses to D_2R, but not D_1R, agonists are enhanced in TAAR1-KO mice. These results indicate that TAAR1 also can exert an inhibitory transcriptional modulation of the D_2R.

Similarly, the profile of striatal postsynaptic signaling events in KO animals is altered only for D_2Rs with selectively activated D_2R-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 D_2R agonist binding affinity (Liu and Li, 2018; Rutigliano et al., 2018). Also, activation of the TAAR1-D_2R heteroreceptor complex in cells negatively modulates beta-arrestin 2–mediated AKT/GSK3β signaling (Harmeier et al., 2015).

An altered presynaptic D_2R 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 D_2R 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 D_2 autoreceptors (Leo et al., 2014). This may involve the existence of TAAR1-D_2R autoreceptor complexes in the mesolimbic DA reward neurons. The removal of the TAAR1 protomer may lead to dysfunction of the D_2R protomer autoreceptor due to altered allosteric receptor-receptor interactions involving recruitment of other receptor protomers and proteins to the D_2 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 D_2Rs 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 D_2R 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-D_2R heteroreceptor complexes in the postjunctional plasma membrane with antagonistic allosteric receptor-receptor interactions (Espinoza et al., 2011; Harmeier et al., 2015) reducing postjunctional D_2R protomer signaling in the ventral striatopallidal GABA antireward neurons. TAAR1 agonists acting at these postjunctional TAAR-D_2 heteroreceptor complexes may, therefore, become novel compounds for treatment of substance use disorder.

Instead, if the TAAR1 agonist used preferentially acts at TAAR1-D_2 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 D_2 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 D_2R with substance abuse is discussed in greater detail subsequently.

A_{2A}-D_2 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, D_2Rs have been the most widely studied target for treatment of drug addiction. The D_2R 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-D_2R interaction in this heteroreceptor complex appears to be a major mechanism for the ability of A_{2A}R to counteract the inhibitory role of D_2R on neuronal excitability and neurotransmitter release, especially in NAC GABA and enkephalin-expressing neurons mediating antireward. These are modulated by antagonistic A_{2A}R-D_2R interactions taking place in heteroreceptor complexes located especially at the dendritic level (Fuxe et al., 2005). These actions within the A_{2A}R-D_2R 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-D_2R 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-D_2R 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-D_2R interactions in the heteroreceptor complexes of the cerebral cortex related to a dominance of D_2 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-D_2R-beta-arrestin-2 heterocomplex which is favored by the antagonistic A_{2A}R-D_2R interaction (Borroto-Escuela et al., 2011). The A_{2A}R agonist favors an enhanced recruitment of beta-arrestin-2 to the D_2R protomer upon D_2R 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 D_2R structure uses a deep binding pocket to bind the atypical antipsychotic drug risperidone (Wang et al., 2018). Instead, D_3 and D_4 receptors bind substituted benzamides with the D_3 or D_4 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 D_2R 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-D_2R interactions in ventral striatum in [^{3}H]raclopride/quinpirole competition experiments (Pintsuk et al., 2016). An A_{2A}R agonist ex vivo reduced the affinity of the D_2R 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 $A_{2A}R$-D_2R and D_2R-sigma1 receptor heterocomplexes in the NAC shell (Borroto-Escuela et al., 2017a). Thus, cocaine self-administration appears to reorganize the $A_{2A}R$-D_2R 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 D_2-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 D_2-like receptor antagonist raclopride, indicating that $A_{2A}R$-D_2R 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 $A_{2A}R$-D_2R 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

D_2RSS is a phenomenon associated with an array of human clinical and/or psychiatric states, 1) being produced by repeated agonist action at D_2R, which 2) promotes multiple reorganizations of the receptor-forming heteromers with adenosine, TAAR1, or other receptor types, 3) alters effects of D_2R 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). D_2RSS 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 D_2RSS, it is now conceivable that D_2RSS 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, Borroto-Escuela, Fuxe, Gainetdinov.

References

Asif-Malik A, Hoener MC, and Canales JJ (2017) Interaction between the trace amine-associated receptor 1 and the dopamine D_2 receptor controls cocaine's neurochemical actions. *Sci Rep* **7**:13901.

Bachtell RK and Self DW (2009) Effects of adenosine A_{2A} receptor stimulation on cocaine-seeking behavior in rats. *Psychopharmacology (Berl)* **206**:469–478.

Barak LS, Salahpour A, Zhang X, Masri B, Sotnikova TD, Ramsey AJ, Violin JD, Lefkowitz RJ, Caron MG, and Gainetdinov RR (2008) Pharmacological characterization of membrane-expressed human trace amine-associated receptor 1 (TAAR1) by a bioluminescence resonance energy transfer cAMP biosensor. *Mol Pharmacol* **74**:585–594.

Berry MD, Gainetdinov RR, Hoener MC, and Shahid M (2017) Pharmacology of human trace amine-associated receptors: therapeutic opportunities and challenges. *Pharmacol Ther* **180**:161–180.

Borowsky B, Adham N, Jones KA, Raddatz R, Artymyshyn R, Ogozalek KL, Durkin MM, Lakhlani PP, Bonini JA, Pathirana S, et al. (2001) Trace amines: identification of a family of mammalian G protein-coupled receptors. *Proc Natl Acad Sci USA* **98**:8966–8971.

Borroto-Escuela DO, Carlsson J, Ambrogini P, Narváez M, Wydra K, Tarakanov AO, Li X, Millón C, Ferraro L, Cuppini R, et al. (2017a) Understanding the role of GPCR heteroreceptor complexes in modulating the brain networks in health and disease. *Front Cell Neurosci* **11**:37.

Borroto-Escuela DO, Narváez M, Wydra K, Pintsuk J, Pinton L, Jimenez-Beristain A, Di Palma M, Jastrzębska J, Filip M, and Fuxe K (2017b) Cocaine self-administration specifically increases $A_{2A}R$-D_2R and D_2R-sigma1R heteroreceptor complexes in the rat nucleus accumbens shell. Relevance for cocaine use disorder. *Pharmacol Biochem Behav* **155**:24–31.

Borroto-Escuela DO, Pintsuk J, Schäfer T, Friedland K, Ferraro L, Tanganelli S, Liu F, and Fuxe K (2016a) Multiple D_2 heteroreceptor complexes: new targets for treatment of schizophrenia. *Ther Adv Psychopharmacol* **6**:77–94.

Borroto-Escuela DO, Romero-Fernandez W, Garriga P, Ciruela F, Narvaez M, Tarakanov AO, Palkovits M, Agnati LF, and Fuxe K (2013) G protein-coupled receptor heterodimerization in the brain. *Methods Enzymol* **521**:281–294.

Borroto-Escuela DO, Romero-Fernandez W, Tarakanov AO, Ciruela F, Agnati LF, and Fuxe K (2011) On the existence of a possible A_{2A}-D_2-β-Arrestin2 complex: A_{2A} agonist modulation of D_2 agonist-induced β-arrestin2 recruitment. *J Mol Biol* **406**:687–699.

Borroto-Escuela DO, Wydra K, Li X, Rodriguez D, Carlsson J, Jastrzębska J, Filip M, and Fuxe K (2018) Disruption of $A_{2A}R$-D_2R heteroreceptor complexes after $A_{2A}R$ transmembrane 5 peptide administration enhances cocaine self-administration in rats. *Mol Neurobiol* **55**:7038–7048.

Borroto-Escuela DO, Wydra K, Pintsuk J, Narvaez M, Corrales F, Zaniewska M, Agnati LF, Franco R, Tanganelli S, Ferraro L, et al. (2016b) Understanding the functional plasticity in neural networks of the basal ganglia in cocaine use disorder: a role for allosteric receptor-receptor interactions in A_{2A}-D_2 heteroreceptor complexes. *Neural Plast* **2016**:4827268.

Bradaia A, Trube G, Stalder H, Norcross RD, Ozmen L, Wettstein JG, Pinard A, Buchy D, Gassmann M, Hoener MC, et al. (2009) The selective antagonist EPPTB reveals TAAR1-mediated regulatory mechanisms in dopaminergic neurons of the mesolimbic system. *Proc Natl Acad Sci USA* **106**:20081–20086.

Brown RW, Flanigan TJ, Thompson KN, Thacker SK, Schaefer TL, and Williams MT (2004a) Neonatal quinpirole treatment impairs Morris water task performance in early postweanling rats: relationship to increases in corticosterone and decreases in neurotrophic factors. *Biol Psychiatry* **56**:161–168.

Brown RW, Gass JT, and Kostrzewa RM (2002) Ontogenetic quinpirole treatments produce spatial memory deficits and enhance skilled reaching in adult rats. *Pharmacol Biochem Behav* **72**:591–600.

Brown RW, Kirby SL, Denton AR, Dose JM, Cummins ED, Drew Gill W, and Burgess KC (2018) An analysis of the rewarding and aversive associative properties of nicotine in the neonatal quinpirole model: effects on glial cell line-derived neurotrophic factor (GDNF). *Schizophr Res* **194**:107–114.

Brown RW, Maple AM, Perna MK, Sheppard AB, Cope ZA, and Kostrzewa RM (2012) Schizophrenia and substance abuse comorbidity: nicotine addiction and the neonatal quinpirole model. *Dev Neurosci* **34**:140–151.

Brown RW, Perna MK, Schaefer TL, and Williams MT (2006) The effects of adulthood nicotine treatment on D_2-mediated behavior and neurotrophins of rats neonatally treated with quinpirole. *Synapse* **59**:253–259.

Brown RW, Thompson KD, Thompson KN, Ward JJ, Thacker SK, Williams MT, and Kostrzewa RM (2004b) Adulthood nicotine treatment alleviates behavioural impairments in rats neonatally treated with quinpirole: possible roles of acetylcholine function and neurotrophic factor expression. *Eur J Neurosci* **19**:1634–1642.

Brown RW, Thompson KN, Click IA, Best RA, Thacker SK, and Perna MK (2005) The effects of eticlopride on Morris water task performance in male and female rats neonatally treated with quinpirole. *Psychopharmacology (Berl)* **180**:234–240.

Brus R, Kostrzewa RM, Nowak P, Perry KW, and Kostrzewa JP (2003) Ontogenetic quinpirole treatments fail to prime for D_2 agonist-enhancement of locomotor activity in 6-hydroxydopamine-lesioned rats. *Neurotox Res* **5**:329–338.

Brus R, Szkilnik R, Nowak P, Kasperska A, Oswiecimska J, Kostrzewa R, and Shani J (1998a) Locomotor sensitization of dopamine receptors by their agonists quinpirole and SKF-38393, during maturation and aging in rats. *Pharmacol Res Commun* **10**:25–30.

Brus R, Szkilnik R, Nowak P, Kostrzewa R, and Shani J (1998b) Sensitivity of central dopamine receptors in rats to quinpirole and SKF-38393, administered at their early stages of ontogenicity, evaluated by learning and memorizing a conditioned avoidance reflex. *Pharmacol Res Commun* **10**:31–36.

Bunzow JR, Sonders MS, Arttamangkul S, Harrison LM, Zhang G, Quigley DI, Darland T, Suchland KL, Pasumamula S, Kennedy JL, et al. (2001) Amphetamine, 3,4-methylenedioxymethamphetamine, lysergic acid diethylamide, and metabolites of the catecholamine neurotransmitters are agonists of a rat trace amine receptor. *Mol Pharmacol* **60**:1181–1188.

Chien EY, Liu W, Zhao Q, Katritch V, Han GW, Hanson MA, Shi L, Newman AH, Javitch JA, Cherezov V, et al. (2010) Structure of the human dopamine D_3 receptor in complex with a D_2/D_3 selective antagonist. *Science* **330**:1091–1095.

Collins GT, Witkin JM, Newman AH, Svensson KA, Grundt P, Cao J, and Woods JH (2005) Dopamine agonist-induced yawning in rats: a dopamine D_3 receptor-mediated behavior. *J Pharmacol Exp Ther* **314**:310–319.

Cope ZA, Huggins KN, Sheppard AB, Noel DM, Roane DS, and Brown RW (2010) Neonatal quinpirole treatment enhances locomotor activation and dopamine

release in the nucleus accumbens core in response to amphetamine treatment in adulthood. *Synapse* **64**:289–300.
Der-Ghazarian T, Gutierrez A, Varela FA, Herbert MS, Amodeo LR, Charntikov S, Crawford CA, and McDougall SA (2012) Dopamine receptor inactivation in the caudate-putamen differentially affects the behavior of preweanling and adult rats. *Neuroscience* **226**:427–440.
Der-Ghazarian T, Widarma CB, Gutierrez A, Amodeo LR, Valentine JM, Humphrey DE, Gonzalez AE, Crawford CA, and McDougall SA (2014) Behavioral effects of dopamine receptor inactivation in the caudate-putamen of preweanling rats: role of the D_2 receptor. *Psychopharmacology (Berl)* **231**:651–662.
Di Cara B, Maggio R, Aloisi G, Rivet JM, Lundius EG, Yoshitake T, Svenningsson P, Brocco M, Gobert A, De Groote L, et al. (2011) Genetic deletion of trace amine 1 receptors reveals their role in auto-inhibiting the actions of ecstasy (MDMA). *J Neurosci* **31**:16928–16940.
Espinoza S, Ghisi V, Emanuele M, Leo D, Sukhanov I, Sotnikova TD, Chieregatti E, and Gainetdinov RR (2015a) Postsynaptic D_2 dopamine receptor supersensitivity in the striatum of mice lacking TAAR1. *Neuropharmacology* **93**:308–313.
Espinoza S, Lignani G, Caffino L, Maggi S, Sukhanov I, Leo D, Mus L, Emanuele M, Ronzitti G, Harmeier A, et al. (2015b) TAAR1 modulates cortical glutamate NMDA receptor function. *Neuropsychopharmacology* **40**:2217–2227.
Espinoza S, Salahpour A, Masri B, Sotnikova TD, Messa M, Barak LS, Caron MG, and Gainetdinov RR (2011) Functional interaction between trace amine-associated receptor 1 and dopamine D_2 receptor. *Mol Pharmacol* **80**:416–425.
Filip M, Zaniewska M, Frankowska M, Wydra K, and Fuxe K (2012) The importance of the adenosine A(2A) receptor-dopamine D(2) receptor interaction in drug addiction. *Curr Med Chem* **19**:317–355.
Fiorentini C, Busi C, Gorruso E, Gotti C, Spano P, and Missale C (2008) Reciprocal regulation of dopamine D_1 and D_3 receptor function and trafficking by heterodimerization. *Mol Pharmacol* **74**:59–69.
Fiorentini C, Busi C, Spano P, and Missale C (2010) Dimerization of dopamine D_1 and D_3 receptors in the regulation of striatal function. *Curr Opin Pharmacol* **10**: 87–92.
Fuxe K and Borroto-Escuela DO (2016) Heteroreceptor complexes and their allosteric receptor–receptor interactions as a novel biological principle for integration of communication in the CNS: targets for drug development. *Neuropsychopharmacology* **41**: 380–382.
Fuxe K, Borroto-Escuela DO, Tarakanov AO, Romero-Fernandez W, Ferraro L, Tanganelli S, Perez-Alea M, Di Palma M, and Agnati LF (2014a) Dopamine D_2 heteroreceptor complexes and their receptor-receptor interactions in ventral striatum: novel targets for antipsychotic drugs. *Prog Brain Res* **211**: 113–139.
Fuxe K, Ferré S, Canals M, Torvinen M, Terasmaa A, Marcellino D, Goldberg SR, Staines W, Jacobsen KX, Lluis C, et al. (2005) Adenosine A_{2A} and dopamine D_2 heteromeric receptor complexes and their function. *J Mol Neurosci* **26**: 209–220.
Fuxe K, Marcellino D, Rivera A, Diaz-Cabiale Z, Filip M, Gago B, Roberts DC, Langel U, Genedani S, Ferraro L, et al. (2008) Receptor-receptor interactions within receptor mosaics. Impact on neuropsychopharmacology. *Brain Res Brain Res Rev* **58**: 415–452.
Fuxe K, Tarakanov A, Romero Fernandez W, Ferraro L, Tanganelli S, Filip M, Agnati LF, Garriga P, Diaz-Cabiale Z, and Borroto-Escuela DO (2014b) Diversity and bias through receptor-receptor interactions in GPCR heteroreceptor complexes. Focus on examples from dopamine D_2 receptor heteromerization. *Front Endocrinol (Lausanne)* **5**:71.
Gainetdinov RR, Bohn LM, Sotnikova TD, Cyr M, Laakso A, Macrae AD, Torres GE, Kim KM, Lefkowitz RJ, Caron MG, et al. (2003) Dopaminergic supersensitivity in G protein-coupled receptor kinase 6-deficient mice. *Neuron* **38**:291–303.
Grandy DK (2007) Trace amine-associated receptor 1-family archetype or iconoclast? *Pharmacol Ther* **116**:355–390.
Harmeier A, Obermueller S, Meyer CA, Revel FG, Buchy D, Chaboz S, Dernick G, Wettstein JG, Iglesias A, Rolink A, et al. (2015) Trace amine-associated receptor 1 activation silences GSK3β signaling of TAAR1 and D_2R heteromers. *Eur Neuropsychopharmacol* **25**:2049–2061.
Kellendonk C, Simpson EH, Polan HJ, Malleret G, Vronskaya S, Winiger V, Moore H, and Kandel ER (2006) Transient and selective overexpression of dopamine D_2 receptors in the striatum causes persistent abnormalities in prefrontal cortex functioning. *Neuron* **49**:603–615.
Kostrzewa RM (1995) Dopamine receptor supersensitivity. *Neurosci Biobehav Rev* **19**:1–17.
Kostrzewa RM and Brus R (1991) Ontogenic homologous supersensitization of quinpirole-induced yawning in rats. *Pharmacol Biochem Behav* **39**:517–519.
Kostrzewa RM, Brus R, and Kalbfleisch J (1991) Ontogenetic homologous sensitization to the antinociceptive action of quinpirole in rats. *Eur J Pharmacol* **209**: 157–161.
Kostrzewa RM, Brus R, Rykaczewska M, and Plech A (1993a) Low-dose quinpirole ontogenically sensitizes to quinpirole-induced yawning in rats. *Pharmacol Biochem Behav* **44**:487–489.
Kostrzewa RM, Guo J, and Kostrzewa FP (1993b) Ontogenetic quinpirole treatment induces vertical jumping activity in rats. *Eur J Pharmacol* **239**:183–187.
Kostrzewa RM, Hamdi A, and Kostrzewa FP (1990) Production of prolonged supersensitization of dopamine D_2 receptors. *Eur J Pharmacol* **183**:1411–1412.
Kostrzewa RM and Kostrzewa FP (2012) Neonatal 6-hydroxydopamine lesioning enhances quinpirole-induced vertical jumping in rats that were quinpirole primed during postnatal ontogeny. *Neurotox Res* **21**:231–235.
Kostrzewa RM, Kostrzewa JP, Brown RW, Nowak P, and Brus R (2008) Dopamine receptor supersensitivity: development, mechanisms, presentation, and clinical applicability. *Neurotox Res* **14**:121–128.
Kostrzewa RM, Kostrzewa JP, Nowak P, Kostrzewa RA, and Brus R (2004) Dopamine D_2 agonist priming in intact and dopamine-lesioned rats. *Neurotox Res* **6**: 457–462.
Kostrzewa RM, Nowak P, Brus R, and Brown RW (2016) Perinatal treatments with the dopamine D_2-receptor agonist quinpirole produces permanent D_2-receptor supersensitization: a model of schizophrenia. *Neurochem Res* **41**:183–192.
Leo D, Mus L, Espinoza S, Hoener MC, Sotnikova TD, and Gainetdinov RR (2014) Taar1-mediated modulation of presynaptic dopaminergic neurotransmission: role of D_2 dopamine autoreceptors. *Neuropharmacology* **81**:283–291.
Leonard S, Mexal S, and Freedman R (2007) Smoking, genetics and schizophrenia: evidence for self medication. *J Dual Diagn* **3**:43–59.
Lindemann L, Meyer CA, Jeanneau K, Bradaia A, Ozmen L, Bluethmann H, Bettler B, Wettstein JG, Borroni E, Moreau JL, et al. (2008) Trace amine-associated receptor 1 modulates dopaminergic activity. *J Pharmacol Exp Ther* **324**:948–956.
Liu JF and Li JX (2018) TAAR1 in addiction: looking beyond the tip of the iceberg. *Front Pharmacol* **9**:279.
Männel B, Jaiteh M, Zeifman A, Randakova A, Möller D, Hübner H, Gmeiner P, and Carlsson J (2017) Structure-guided screening for functionally selective D_2 dopamine receptor ligands from a virtual chemical library. *ACS Chem Biol* **12**: 2652–2661.
Maple AM, Perna MK, Parlaman JP, Stanwood GD, and Brown RW (2007) Ontogenetic quinpirole treatment produces long-lasting decreases in the expression of *Rgs9*, but increases *Rgs17* in the striatum, nucleus accumbens and frontal cortex. *Eur J Neurosci* **26**:2532–2538.
Maple AM, Smith KJ, Perna MK, and Brown RW (2015) Neonatal quinpirole treatment produces prepulse inhibition deficits in adult male and female rats. *Pharmacol Biochem Behav* **137**:93–100.
Marcellino D, Ferré S, Casadó V, Cortés A, Le Foll B, Mazzola C, Drago F, Saur O, Stark H, Soriano A, et al. (2008) Identification of dopamine D_1-D_3 receptor heteromers. Indications for a role of synergistic D_1-D_3 receptor interactions in the striatum. *J Biol Chem* **283**:26016–26025.
Marinelli M, Cooper DC, Baker LK, and White FJ (2003) Impulse activity of midbrain dopamine neurons modulates drug-seeking behavior. *Psychopharmacology (Berl)* **168**:84–98.
McDougall SA, Eaton SE, Mohd-Yusof A, and Crawford CA (2015) Age-dependent changes in cocaine sensitivity across early ontogeny in male and female rats: possible role of dorsal striatal D_2^{High} receptors. *Psychopharmacology (Berl)* **232**: 2287–2301.
McDougall SA, Valentine JM, Gonzalez AE, Humphrey DE, Widarma CB, and Crawford CA (2014) Behavioral effects of dopamine receptor inactivation during the adolescent period: age-dependent changes in dorsal striatal D_2^{High} receptors. *Psychopharmacology (Berl)* **231**:1637–1647.
Moody CA and Spear LP (1992) Ontogenetic differences in the psychopharmacological responses to separate and combined stimulation of D_1 and D_2 dopamine receptors during the neonatal to weanling age period. *Psychopharmacology (Berl)* **106**:161–168.
Nowak P, Brus R, and Kostrzewa RM (2001) Amphetamine-induced enhancement of neostriatal in vivo microdialysate dopamine content in rats, quinpirole-primed as neonates. *Pol J Pharmacol* **53**:319–329.
O'Neill CE, LeTendre ML, and Bachtell RK (2012) Adenosine A_{2A} receptors in the nucleus accumbens bi-directionally alter cocaine seeking in rats. *Neuropsychopharmacology* **37**:1245–1256.
Oswiecimska J, Brus R, Szkilnik R, Nowak P, and Kostrzewa RM (2000) 7-OH-DPAT, unlike quinpirole, does not prime a yawning response in rats. *Pharmacol Biochem Behav* **67**:11–15.
Pei Y, Asif-Malik A, and Canales JJ (2016) Trace amines and the trace amine-associated receptor 1: pharmacology, neurochemistry, and clinical implications. *Front Neurosci* **10**:148.
Perna MK and Brown RW (2013) Adolescent nicotine sensitization and effects of nicotine on accumbal dopamine release in a rodent model of increased dopamine D_2 receptor sensitivity. *Behav Brain Res* **242**:102–109.
Perna MK, Cope ZA, Maple AM, Longacre ID, Correll JA, and Brown RW (2008) Nicotine sensitization in adult male and female rats quinpirole-primed as neonates. *Psychopharmacology (Berl)* **199**:67–75.
Peterson DJ, Gill WD, Dose JM, Hoover DB, Pauly JR, Cummins ED, Burgess KC, and Brown RW (2017) The effects of nicotine in the neonatal quinpirole rodent model of psychosis: neural plasticity mechanisms and nicotinic receptor changes. *Behav Brain Res* **325**:17–24.
Pintsuk J, Borroto-Escuela DO, Pomierny B, Wydra K, Zaniewska M, Filip M, and Fuxe K (2016) Cocaine self-administration differentially affects allosteric A_{2A}-D_2 receptor-receptor interactions in the striatum. Relevance for cocaine use disorder. *Pharmacol Biochem Behav* **144**:85–91.
Plech A, Brus R, Kalbfleisch JH, and Kostrzewa RM (1995) Enhanced oral activity responses to intrastriatal SKF 38393 and m-CPP are attenuated by intrastriatal mianserin in neonatal 6-OHDA-lesioned rats. *Psychopharmacology (Berl)* **119**: 466–473.
Prieto GA, Perez-Burgos A, Fiordelisio T, Salgado H, Galarraga E, Drucker-Colin R, and Bargas J (2009) Dopamine D_2-class receptor supersensitivity as reflected in Ca^{2+} current modulation in neostriatal neurons. *Neuroscience* **164**:345–350.
Revel FG, Moreau JL, Gainetdinov RR, Bradaia A, Sotnikova TD, Mory R, Durkin S, Zbinden KG, Norcross R, Meyer CA, et al. (2011) TAAR1 activation modulates monoaminergic neurotransmission, preventing hyperdopaminergic and hypoglutamatergic activity. *Proc Natl Acad Sci USA* **108**:8485–8490.
Revel FG, Moreau JL, Gainetdinov RR, Ferragud A, Velázquez-Sánchez C, Sotnikova TD, Morairty SR, Harmeier A, Groebke Zbinden K, Norcross RD, et al. (2012) Trace amine-associated receptor 1 partial agonism reveals novel paradigm for neuropsychiatric therapeutics. *Biol Psychiatry* **72**:934–942.
Revel FG, Moreau JL, Pouzet B, Mory R, Bradaia A, Buchy D, Metzler V, Chaboz S, Groebke Zbinden K, Galley G, et al. (2013) A new perspective for schizophrenia: TAAR1 agonists reveal antipsychotic- and antidepressant-like activity, improve cognition and control body weight. *Mol Psychiatry* **18**:543–556.
Rutigliano G, Accorroni A, and Zucchi R (2018) The case for TAAR1 as a modulator of central nervous system function. *Front Pharmacol* **8**:987.

Seeman P, Ko F, Jack E, Greenstein R, and Dean B (2007) Consistent with dopamine supersensitivity, RGS9 expression is diminished in the amphetamine-treated animal model of schizophrenia and in postmortem schizophrenia brain. *Synapse* **61**: 303–309.

Seutin V, Verbanck P, Massotte L, and Dresse A (1991) Acute amphetamine-induced subsensitivity of A10 dopamine autoreceptors in vitro. *Brain Res* **558**:141–144.

Sheppard B, Lehmann J, Cope ZA, and Brown RW (2009) Sex differences in nicotine sensitization and conditioned hyperactivity in adolescent rats neonatally treated with quinpirole: role of D_2 and D_3 receptor subtypes. *Behav Neurosci* **123**: 1296–1308.

Soria G, Castañé A, Ledent C, Parmentier M, Maldonado R, and Valverde O (2006) The lack of A_{2A} adenosine receptors diminishes the reinforcing efficacy of cocaine. *Neuropsychopharmacology* **31**:978–987.

Spear LP (1979) The use of psychopharmacological procedures to analyse the ontogeny of learning and retention: issues and concerns, in *Ontogeny of Learning and Memory* (Spear NE and Campbell BA eds) pp 135–156, Lawrence Erlbaum Associates, Hillsdale, NJ.

Spear LP (2000) The adolescent brain and age-related behavioral manifestations. *Neurosci Biobehav Rev* **24**:417–463.

Stephenson T (2005) How children's responses to drugs differ from adults. *Br J Clin Pharmacol* **59**:670–673.

Strömberg I, Popoli P, Müller CE, Ferré S, and Fuxe K (2000) Electrophysiological and behavioural evidence for an antagonistic modulatory role of adenosine A_{2A} receptors in dopamine D_2 receptor regulation in the rat dopamine-denervated striatum. *Eur J Neurosci* **12**:4033–4037.

Tammimäki A, Pietilä K, Raattamaa H, and Ahtee L (2006) Effect of quinpirole on striatal dopamine release and locomotor activity in nicotine-treated mice. *Eur J Pharmacol* **531**:118–125.

Thacker SK, Perna MK, Ward JJ, Schaefer TL, Williams MT, Kostrzewa RM, and Brown RW (2006) The effects of adulthood olanzapine treatment on cognitive performance and neurotrophic factor content in male and female rats neonatally treated with quinpirole. *Eur J Neurosci* **24**:2075–2083.

Tizabi Y, Copeland RL Jr, Brus R, and Kostrzewa RM (1999) Nicotine blocks quinpirole-induced behavior in rats: psychiatric implications. *Psychopharmacology (Berl)* **145**:433–441.

Trifilieff P, Rives ML, Urizar E, Piskorowski RA, Vishwasrao HD, Castrillon J, Schmauss C, Slättman M, Gullberg M, and Javitch JA (2011) Detection of antigen interactions ex vivo by proximity ligation assay: endogenous dopamine D_2-adenosine A_{2A} receptor complexes in the striatum. *Biotechniques* **51**:111–118.

Urs NM, Gee SM, Pack TF, McCorvy JD, Evron T, Snyder JC, Yang X, Rodriguiz RM, Borrelli E, Wetsel WC, et al. (2016) Distinct cortical and striatal actions of a β-arrestin-biased dopamine D_2 receptor ligand reveal unique antipsychotic-like properties. *Proc Natl Acad Sci USA* **113**:E8178–E8186.

Wall CA, Croarkin PE, Swintak C, and Koplin BA (2012) Psychiatric pharmacogenomics in pediatric psychopharmacology. *Child Adolesc Psychiatr Clin N Am* **21**: 773–788.

Wang S, Che T, Levit A, Shoichet BK, Wacker D, and Roth BL (2018) Structure of the D_2 dopamine receptor bound to the atypical antipsychotic drug risperidone. *Nature* **555**:269–273.

Wang S, Wacker D, Levit A, Che T, Betz RM, McCorvy JD, Venkatakrishnan AJ, Huang XP, Dror RO, Shoichet BK, et al. (2017) D_4 dopamine receptor high-resolution structures enable the discovery of selective agonists. *Science* **358**:381–386.

Winterer G (2010) Why do patients with schizophrenia smoke? *Curr Opin Psychiatry* **23**:112–119.

Wolinsky TD, Swanson CJ, Smith KE, Zhong H, Borowsky B, Seeman P, Branchek T, and Gerald CP (2007) The trace amine 1 receptor knockout mouse: an animal model with relevance to schizophrenia. *Genes Brain Behav* **6**:628–639.

Wydra K, Gołembiowska K, Suder A, Kamińska K, Fuxe K, and Filip M (2015a) On the role of adenosine A_{2A} receptors in cocaine-induced reward: a pharmacological and neurochemical analysis in rats. *Psychopharmacology (Berl)* **232**:421–435.

Wydra K, Suder A, Borroto-Escuela DO, Filip M, and Fuxe K (2015b) On the role of A_{2A} and D_2 receptors in control of cocaine and food-seeking behaviors in rats. *Psychopharmacology (Berl)* **232**:1767–1778.

Zhen X, Torres C, Cai G, and Friedman E (2002) Inhibition of protein tyrosine/mitogen-activated protein kinase phosphatase activity is associated with D_2 dopamine receptor supersensitivity in a rat model of Parkinson's disease. *Mol Pharmacol* **62**:1356–1363.

Address correspondence to: Dr. Richard M. Kostrzewa, Department of Biomedical Sciences, Quillen College of Medicine, East Tennessee State University, P.O. Box 70577, Johnson City, TN 37614. E-mail: kostrzew@etsu.edu