Published in final edited form as:

Life Sci. 2008 July 4; 83(1-2): 74–78.

Strain Differences in the Expression of Dopamine D1 Receptors in Wistar-Kyoto (WKY) and Wistar Rats

Andrew Novick, Irene Yaroslavsky, and Shanaz Tejani-Butt *

Department of Pharmaceutical Sciences, University of the Sciences in Philadelphia, 600 S. 43rd St, Philadelphia, PA 19104

Abstract

The Wistar-Kyoto (WKY) rat is a stress-sensitive strain that is prone to depressive-like behavior in various experimental paradigms. While recent work has highlighted a role for dopamine (DA) in the pathology of depression, research on the WKY rat has also suggested that dysfunction of DA pathways may be an important component of the behavior in this strain. Previous work has demonstrated differential patterns of dopamine transporter sites, dopamine D2 and D3 receptors in the WKY rats compared to control strains. To further this work, the present study utilized autoradiographic analysis of [³H]-SCH23390 binding to DA D1 receptors in various brain regions of naïve male WKY and Wistar (WIS) rats. The results revealed a significant strain difference, with WKY rats demonstrating lower D1 binding in the caudate putamen and regions of the nucleus accumbens ($p < 0.05$). An opposite pattern was found in the substantia nigra pars reticulata where D1 binding was higher in WKY rats compared to WIS rats ($p < 0.05$). Because the D1 receptor represents a critical site where DA acts to modify behavior related to depression, the altered expression of this receptor in the WKY rat found in the present study may be reflective of the depressive susceptibility noted in this strain.

Introduction

Dopamine (DA) in the Central Nervous System plays an important role in facilitating psychomotor speed, motivation, reward, and cognition. These behaviors are often disrupted in depression, and despite a traditional focus on serotonin (5-HT) and norepinephrine (NE), evidence from both humans and animals suggests that dysfunction of DA pathways may be a critical component of the neurobiological basis of depression (Dunlop and Nemeroff, 2007).

With regard to animal research, the Wistar-Kyoto (WKY) rat has been proposed as a putative animal model of depression (Pare, 1989; Malkesman et al., 2006). When compared to other strains, the WKY rat is more susceptible to despair-like behavior in the Learned Helplessness procedure (LH) and the Forced Swim Test (FST), demonstrates less activity in the Open Field Test (OFT) and is prone to freezing and passive behavior in a variety of other experimental paradigms (Paré, 1993 and 1994a). Besides evidence of an altered hypothalamic-pituitary-adrenal axis (Redei et al, 1994) and deficient NE transmission (Pardon et al., 2002; Tejani-Butt et al., 1994), several lines of evidence suggest dysfunctional DA transmission in the WKY. Similar to the symptom of anhedonia commonly found in depression and attributed to reduced

*Corresponding author s.tejani@usip.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

DA function, these rats appear to display reduced interest in pleasurable activities, such as reduced saccharin consumption (Malkesman et al., 2005), reduced levels of social play (Malkesman et al., 2006), less investigatory behavior towards female rats (Paré, 2000), reduced responding for sucrose (De la Garza, 2005) and reduced consumption of food in a novel environment (Paré, 1994b). While WKY rats are largely unresponsive to 5-HT re-uptake blockade (López-Rubalcava and Lucki, 2000; Griebel et al., 1999) they demonstrate significant increases in performance in tests of emotionality following administration of drugs that block DA/NE re-uptake (Tejani-Butt et al., 2003; Pare et al., 2001; Drolet et al., 2002), highlighting a possible role for DA in WKY behavioral pathology.

Our lab has also demonstrated differences in DA transporter (DAT), DA D2 and D3 receptor binding in the WKY rat compared to control strains, suggesting altered DA transmission (Jiao et al., 2003; Yaroslavsky et al., 2006). This is supported by a separate group that found reduced DA levels in the pre-frontal cortex (PFC) and increased DA turnover in the nucleus accumbens (NAc) and striatum compared to Wistar (WIS) controls (De la Garza and Mahoney, 2004).

While the DAT along with D2 and D3 receptors play important roles in regulating DA transmission, the DA D1 receptor may represent a critical site where DA acts to modify behavior related to depression. For example, selective D1 agonists have antidepressant effects in both LH and the FST, while blockade of D1 receptors prevents the antidepressant effect of imipramine as well as other agents (D'Aquila et al., 1994; Gambarana et al., 1995; Takamori et al., 2001).

High numbers of D1 receptors are located within Caudate Putamen (CPu), Nucleus Accumbens (NAc), and Substantia Nigra pars reticulata (SNr) with a less dense distribution in the amygdaloid regions (Savasta et al., 1986). Evidence suggests D1 receptors in the CPu, NAc, and SNr facilitate motivated behavior (Norwend et al., 2001; Trevitt et al., 2001), while those in the amygdala are more involved with learning, memory and fear (Macedo et al., 2007; Guarracci et al., 1999). Given the potential importance of the D1 receptor in depressive behavior, together with evidence suggesting altered DA transmission in the WKY rat, the present study sought to measure central D1 binding in the CPu, NAc, SNr, and amygdala in WKY and WIS rats using quantitative autoradiographic technique.

Methods

Animals

Male WKY and Wistar rats, 8 months of age were used in this study (n=6 in each strain). WKY rats were obtained from the breeding colony at VA Medical Center (Perry Point, MD) originally from breeding stock from Charles River Laboratories (Kingston, NY). Wistar rats were purchased from Harlan (Indianapolis, IN) and given a two week habituation period to the new environment before use in the experiment. Animals were individually housed at 22°C and placed on a 12-hr light/dark cycle. Food and water were kept available during the whole day.

Brain section preparation

Animals were decapitated between 8:00 and 10:00 a.m. and the brains were removed immediately and stored at -80°C until use. Brain sections (16µm) were cut at -18°C in a cryostat microtome and mounted on gelatin-coated microscope slides. Before storing at -80°C, all slides were kept overnight at 4°C under vacuum. Sections were cut from Plate 12 (caudate putamen (CPu) and nucleus accumbens (NAc)), Plate 30 (basolateral amygdala (BLA), lateral amygdala (LA), and intercalated nuclei (I)) and Plate 42 (substantia nigra pars reticulata (SNr)) according to the Brain Atlas of Paxinos and Watson (1998). One slide from each Plate per animal (consisting of two consecutive brain sections) was used for autoradiographic analysis.

D1 receptor binding

D1 receptors were labeled with [^3H]-SCH23390 using the procedure described by Savasta et al. (1986) with minor modifications. Specifically, sections were preincubated for 15 minutes in a 7.4 pH buffer solution containing 50mM Tris-HCl, 120mM NaCl, 5mM KCl, and 1mM MgCl_2 at room temperature. The sections were then incubated for 60 minutes at room temperature in a similar buffer solution with the addition of 1.5nM [^3H]-SCH23390 (PerkinElmer) and 30nM ketanserin tartrate (Sigma-Aldrich) to block 5-HT $_2$ receptors. Non-specific binding was determined with the addition of 1 μM (+)-butaclamol (Sigma-Aldrich). The incubation was ended by dipping the slides in ice-cold buffer, followed by two consecutive 10 minute washes in ice-cold buffer and a final dip in cold de-ionized water. The sections were then dried at room temperature and transferred into cassettes and exposed to Kodak BioMax MS film with [^3H] standards. The exposure times were 21, 35, and 49 days for plates 12, 42, and 30 respectively.

Quantification and Statistics

The films were analyzed with a computerized brain image analysis system (Brain 3.0) (Gustafson, 1995). Nonspecific binding was subtracted from the total binding to provide the specific binding in the regions of interest.

Statistical analysis was performed using Sigma Stat for Windows. Data were expressed as mean $\pm$ S.E.M specific binding (fmol/mg brain protein). The data in each region of interest were analyzed by a Student's *t*-test. The level of significance was set a priori at $p < 0.05$.

Results

D1 receptor binding in WKY and WIS rats

Binding of [^3H]-SCH23390 to D1 receptor sites in the CPu was lower in WKY rats compared to WIS rats ($t(10) = -3.206$, $p < 0.05$; Fig. 1). A similar strain difference was found in both the core ($t(10) = -2.287$, $p < 0.05$) and shell ($t(10) = -2.833$, $p < 0.05$) of the NAc, with WKY rats demonstrating lower D1 binding than WIS rats (Fig. 2). An opposite pattern was observed in the SNr, in which D1 receptor binding was higher in WKY rats compared to WIS rats ($t(8) = -7.593$, $p < 0.05$; Fig. 3). Regions of the amygdala, including the LA, BLA, and I, failed to show significant strain differences (data not shown).

Discussion

The present results demonstrate a significant strain difference in D1 receptor binding between WKY and WIS rats. Specifically, WKY rats showed decreased binding in the CPu and NAc with increased binding in the SNr compared to WIS rats while no differences were found in amygdaloid regions.

D1 Binding in the Nucleus Accumbens and Caudate Putamen

Evidence suggests that the NAc and CPu act as an interface between motivation and motor activation (Mogenson et al., 1980; Sotak et al., 2005), with DA in these regions invigorating approach responses towards reward or safety (Ikemoto and Panksepp, 1999). Given our previous findings on the strain differences between WKY and WIS rats in terms of DAT, DA-2, and DA-3 receptors along with the behavioral profile and of the WKY rat, we have hypothesized that WKY rats may have a dopaminergic deficit (Jiao et al., 2003; Yaroslavsky, et al., 2006). When taken in the context of these previous studies, the decreased D1 binding in WKY rats found in the CPu and NAc might further reflect a potential deficit in post-synaptic DA activity. Activation of post-synaptic D1 receptors in the CPu and NAc is associated with the phosphorylation of DA- and cAMP-regulated phosphoprotein (DARPP-32), which appears

to be a key modulator of behaviors related to reward, locomotor activity, and response to 5-HT re-uptake inhibitors (Svenningsson et al., 2004). Thus, decreased D1 activity may play a role in the noted impairment of motivated behavior in this strain.

The results of the present study are in agreement with other work comparing D1 binding between rat strains of differing behavioral characteristics. The Roman High Avoidance/Roman Low Avoidance (RHA/RLA) rat strains share a similar behavioral dichotomy with the WIS/WKY strains. Like WKY rats, RLA rats have been proposed as a model for depression (Steimer et al., 2007), display exaggerated neuroendocrine responses to stress, and demonstrate an overall “passive coping style” with less exploratory behavior and increased freezing on various tests compared to their RHA peers (Steimer and Driscoll, 2003). Also, like the WKY rats in the present study, RLA rats have lower D1 binding in the NAc shell, which was interpreted to reflect lower post-synaptic dopaminergic function (Guitart-Masip et al., 2003). A similar result comes from comparing Sprague Dawley (SD) rats with high and low locomotor responses to novelty (Hooks et al., 1994). The low responders demonstrated lower D1 binding in the NAc, which was again interpreted to reflect lower post-synaptic DA activity.

From the above studies, along with the present results, it is tempting to speculate a relationship between low D1 binding and depressive behavioral characteristics. Further evidence for such a relationship comes from the finding that while acute treatment with a D1 agonist in SD rats prevents escape deficit in the LH procedure, prior chronic treatment with the agonist can actually produce helpless behavior (Gambara et al., 1995). The chronic agonist treatment was associated with a significant decrease in D1 binding in the PFC. While this study only measured D1 binding in the PFC, a separate study found lower D1 binding in the CPu and NAc of SD rats that were susceptible to LH versus those that were resistant (Kram et al., 2002). Thus, it is possible that the lower D1 binding found in WKY rats compared to WIS rats in the NAc and CPu may be related to their differing susceptibilities to LH.

It should be noted, however, that one study found that SD rats have lower D1 binding in the CPu and NAc and demonstrate decreased immobility responses compared to WIS rats (Zamudio et al., 2005). Decreased D1 binding in the NAc and CPu in the context of decreased immobility would appear to contradict a proposed relationship between low D1 binding and depressive-like behavior. Besides the many other neurochemical factors that contribute to emotional behavior, this result may be due to a possible independence of D1 binding from both DA levels and receptor sensitivity. For example, DA depletion with reserpine for five days fails to alter central D1 binding (Missale et al., 1989). Furthermore, while chronic antidepressant treatment decreases D1 binding in limbic regions (Klimek and Nielson, 1987) it potentiates the behavioral response to DA agonists (Serra et al., 1990). This phenomenon is likely due to antidepressant induced increases in D1 associated G_{olf} protein levels (Taoka et al., 2006) and adenylyl cyclase V_{max} (De Montis et al., 1990). Therefore, while much evidence supports a link between the lower D1 binding in the CPu and NAc of WKY rats found in the present study and their susceptibility to depressive-like behavior, other variables connected to D1 function (such as sensitivity, G-proteins, and basal DA levels) may be involved as well.

D1 Binding in the Amygdala

Previously, we found WKY rats to have lower DAT binding in the lateral, medial, and central amygdala compared to control strains (Jiao et al., 2003). The current results showed no differences in D1 binding between WKY and WIS rats in any of the regions measured (BLA, LA, I). Interestingly, a post-mortem study utilizing depressed and healthy human subjects also found decreased DAT binding in the amygdala of depressed individuals without any differences in D1 binding (Klimek et al., 2003). RHA/RLA rats also fail to show any differences in D1 binding in amygdaloid regions (Guitart-Masip et al., 2003). Therefore, it is possible that

D1 binding may not be indicative of differences in DA activity in the amygdala amongst the two strains studied.

D1 Binding in the Substantia Nigra

The SNr contains D1 receptors located on the pre-synaptic terminal axons of neurons originating in the CPu and NAc (Missale et al., 1998). Similar to post-synaptic D1 receptors in the CPu and NAc, stimulation of these pre-synaptic D1 receptors in the SNr is associated with motivated behavior, as blockade of D1 receptors in both SNr and NAc/CPu induces similar reductions in operant lever pressing and OFT activity (Trevitt et al., 2001).

With regard to the differences in D1 binding found in the present study, Siemiakowski et al. (2000) demonstrated a positive correlation between D1 binding in the SNr and locomotor activity in the OFT in WIS rats. Because D1 agonists injected into the SNr have been found to increase motor activity (Trevitt et al., 2002), it is possible that WIS rats with high D1 binding have higher DA tone which facilitates activity in the OFT. However, in the present study, SNr D1 receptor binding was significantly higher in WKY rats compared to WIS rats, yet WKY rats consistently demonstrate lower OFT activity than WIS rats (Paré, 1994; Tejani-Butt et al., 2003). In attempting to reconcile these findings, it may be important to consider that WKY rats have lower levels of DAT binding in the SNr compared to WIS rats, which might reflect an adaptation to lower somatodendritically released DA from the DA containing neurons of the pars compacta (Jiao et al., 2003). If this is the case, higher D1 receptor binding in WKY rats might not represent high DA tone so much as an adaptation to low DA levels in the SN. Alternatively, higher D1 binding in the SNr of WKY rats could reflect enhanced DA activity in this area that facilitates increased fear reactivity in the WKY rat rather than OFT activity. For example, it has been found that D1 receptors in the SNr are involved in mediating the startle response (Meloni and Davis, 2004). As noted in the introduction, WKY rats are prone to freezing behavior and have been shown to demonstrate a higher startle response compared to other strains (Glowa and Hansen, 1994). Further research will be necessary to determine the role of SNr D1 receptors in the behavior of WKY rats and the functional consequences of the increased binding found in the present results.

Conclusions

Perturbations in DA transmission are likely to contribute to the pathology of depression. The WKY rat is an animal model of depressive behavior with potential dysfunction of DA pathways. The present study contributes to our previous work on the WKY rat, demonstrating significant differences in the binding density of the D1 receptor in various brain regions compared to WIS controls. As previous research has demonstrated a role for the D1 receptor in mediating antidepressant response and susceptibility to LH, elucidating the significance of altered D1 receptor expression in WKY rats deserves further study.

Acknowledgements

This study was supported by USPHS grant MH63002 (ST-B) and research funds from the Office of Research and Development, Medical Research Service, Department of Veteran Affairs (W. P.). The authors would like to thank Dr. Xilu Jiao for her helpful assistance with the preparations for this study and Dr. William Paré for generously providing the animals used.

References

- D'Aquila PS, Collu M, Pani L, Gessa GL, Serra G. Antidepressant-like effect of selective dopamine DA-1 receptor agonists in the behavioural despair animal model of depression. *European Journal of Pharmacology* 1994;262(1-2):107-11. [PubMed: 7813561]
- De la Garza R. Wistar Kyoto rats exhibit reduced sucrose pellet reinforcement behavior and intravenous nicotine self-administration. *Pharmacology Biochemistry and Behavior* 2005;82(2):330-7.

- De La Garza R, Mahoney JJ. A distinct neurochemical profile in WKY rats at baseline and in response to acute stress: implications for animal models of anxiety and depression. *Brain Research* 2004;1021(2):209–18. [PubMed: 15342269]
- De Montis GM, Devoto P, Gessa GL, Porcella A, Serra G, Tagliamonte A. Selective adenylate cyclase increase in the limbic area of long-term imipramine-treated rats. *European Journal of Pharmacology* 1990;180(1):169–74. [PubMed: 2194824]
- Drolet G, Proulx K, Pearson D, Rochford J, Deschepper CF. Comparisons of behavioral and neurochemical characteristics between WKY, WKHA, and Wistar rat strains. *Neuropsychopharmacology* 2002;27(3):400–9. [PubMed: 12225697]
- Dunlop BW, Nemeroff CB. The role of dopamine in the pathophysiology of depression. *Archives of General Psychiatry* 2007;64(3):327–37. [PubMed: 17339521]
- Gambarana C, Ghiglieri O, Tagliamonte A, D'Alessandro N, de Montis MG. Crucial role of DA-1 dopamine receptors in mediating the antidepressant effect of imipramine. *Pharmacology Biochemistry and Behavior* 1995a;50(2):147–51.
- Gambarana C, Ghiglieri O, Graziella de Montis M. Desensitization of the DA-1 dopamine receptors in rats reproduces a model of escape deficit reverted by imipramine, fluoxetine and clomipramine. *Progress in Neuropsychopharmacology and Biological Psychiatry* 1995b;19(5):741–55.
- Glowa JR, Hansen CT. Differences in response to an acoustic startle stimulus among forty-six rat strains. *Behavior Genetics* 1994;24(1):79–84. [PubMed: 8192623]
- Griebel G, Cohen C, Perrault G, Sanger DJ. Behavioral effects of acute and chronic fluoxetine in Wistar-Kyoto rats. *Physiology and Behavior* 1999;67(3):315–20. [PubMed: 10497947]
- Guitart-Masip M, Johansson B, Fernández-Teruel A, Cañete T, Tobeña A, Terenius L, Giménez-Llort L. Divergent anatomical pattern of DA-1 and D3 binding and dopamine- and cyclic AMP-regulated phosphoprotein of 32 kDa mRNA expression in the Roman rat strains: Implications for drug addiction. *Neuroscience* 2006;142(4):1231–43. [PubMed: 17008016]
- Gustafson C. Brain software for autoradiography, Version 3.0. 1995
- Guarraci FA, Frohardt RJ, Kapp BS. Amygdaloid D1 dopamine receptor involvement in Pavlovian fear conditioning. *Brain Research* 1999;827(1–2):28–40. [PubMed: 10320690]
- Hooks MS, Juncos JL, Justice JB, Meiergerd SM, Povlock SL, Schenk JO, Kalivas PW. Individual locomotor response to novelty predicts selective alterations in DA-1 and D2 receptors and mRNAs. *Journal of Neuroscience* 1994;14(10):6144–52. [PubMed: 7931568]
- Ikemoto S, Panksepp J. The role of nucleus accumbens dopamine in motivated behavior: a unifying interpretation with special reference to reward-seeking. *Brain Research Reviews* 1999;31(1):6–41. [PubMed: 10611493]
- Jiao X, Paré WP, Tejani-Butt S. Strain differences in the distribution of dopamine transporter sites in rat brain. *Progress in Neuropsychopharmacology and Biological Psychiatry* 2003;27(6):913–9.
- Klimek V, Nielsen M. Chronic treatment with antidepressants decreases the number of [3H]SCH 23390 binding sites in the rat striatum and limbic system. *European Journal of Pharmacology* 1987;139(2):163–9. [PubMed: 3308491]
- Klimek V, Schenck JE, Han H, Stockmeier CA, Ordway GA. Dopaminergic abnormalities in amygdaloid nuclei in major depression: a postmortem study. *Biological Psychiatry* 2002;52(7):740–8. [PubMed: 12372665]
- López-Rubalcava C, Lucki I. Strain differences in the behavioral effects of antidepressant drugs in the rat forced swimming test. *Neuropsychopharmacology* 2000;22(2):191–9. [PubMed: 10649831]
- Macedo CE, Martinez RC, Albrechet-Souza L, Molina VA, Brandão ML. 5-HT₂- and D1-mechanisms of the basolateral nucleus of the amygdala enhance conditioned fear and impair unconditioned fear. *Behavioural Brain Research* 2007;177(1):100–8.
- Malkesman O, Braw Y, Zagoory-Sharon O, Golan O, Lavi-Avnon Y, Schroeder M, Overstreet DH, Yadid G, Weller A. Reward and anxiety in genetic animal models of childhood depression. *Behavioural Brain Research* 2005;164(1):1–10. [PubMed: 16055204]
- Malkesman O, Braw Y, Maayan R, Weizman A, Overstreet DH, Shabat-Simon M, Kesner Y, Touati-Werner D, Yadid G, Weller A. Two different putative genetic animal models of childhood depression. *Biological Psychiatry* 2006;59(1):17–23. [PubMed: 16095569]

- Meloni EG, Davis M. The substantia nigra pars reticulata mediates the enhancement of startle by the dopamine DA-1 receptor agonist SKF 82958 in rats. *Psychopharmacology (Berl)* 2004;174(2):228–36. [PubMed: 14735289]
- Missale C, Nisoli E, Liberini P, Rizzonelli P, Memo M, Buonamici M, Rossi A, Spano P. Repeated reserpine administration up-regulates the transduction mechanisms of DA-1 receptors without changing the density of [3H]SCH 23390 binding. *Brain Research* 1989;483(1):117–22. [PubMed: 2565146]
- Missale C, Nash SR, Robinson SW, Jaber M, Caron MG. Dopamine receptors: from structure to function. *Physiological Reviews* 1998;78(1):189–225. [PubMed: 9457173]
- Mogenson GJ, Jones DL, Yim CY. From motivation to action: functional interface between the limbic system and the motor system. *Progress in Neurobiology* 1980;14(2–3):69–97. [PubMed: 6999537]
- Nowend KL, Arizzi M, Carlson BB, Salamone JD. D1 or D2 antagonism in nucleus accumbens core or dorsomedial shell suppresses lever pressing for food but leads to compensatory increases in chow consumption. *Pharmacology Biochemistry and Behavior* 2001;69(3–4):373–82.
- Pardon MC, Gould GG, Garcia A, Phillips L, Cook MC, Miller SA, Mason PA, Morilak DA. Stress reactivity of the brain noradrenergic system in three rat strains differing in their neuroendocrine and behavioral responses to stress: implications for susceptibility to stress-related neuropsychiatric disorders. *Neuroscience* 2002;115(1):229–42. [PubMed: 12401336]
- Paré WP. “Behavioral despair” test predicts stress ulcer in WKY rats. *Physiology and Behavior* 1989;46(3):483–7. [PubMed: 2623074]
- Paré WP. Passive-avoidance behavior in Wistar-Kyoto (WKY), Wistar, and Fischer-344 rats. *Physiology and Behavior* Nov;1993 54(5):845–52. [PubMed: 8248372]
- Paré WP. Open field, learned helplessness, conditioned defensive burying, and forced-swim tests in WKY rats. *Physiology and Behavior* Mar;1994a 1994 55(3):433–9.
- Paré WP. Hyponeophagia in Wistar Kyoto (WKY) rats. *Physiology and Behavior* 1994b;55(5):975–8.
- Paré WP. Investigatory behavior of a novel conspecific by Wistar Kyoto, Wistar and Sprague-Dawley rats. *Brain Research Bulletin* 2000;53(6):759–65. [PubMed: 11179840]
- Paré WP, Tejani-Butt S, Kluczynski J. The emergence test: effects of psychotropic drugs on neophobic disposition in Wistar Kyoto (WKY) and Sprague Dawley rats. *Progress in Neuropsychopharmacology and Biological Psychiatry* 2001;25(8):1615–28.
- Paxinos, G.; Watson, C. *The Rat Brain in Stereotaxic Coordinates*. 4th ed.. Academic Press; New York: 1998. G.
- Redei E, Paré WP, Aird F, Kluczynski J. Strain differences in hypothalamic-pituitary-adrenal activity and stress ulcer. *American Journal of Physiology* 1994;266(2 Pt 2):R353–60. [PubMed: 8141389]
- Richtand NM, Woods SC, Berger SP, Strakowski SM. D3 dopamine receptor, behavioral sensitization, and psychosis. *Neuroscience and Biobehavioral Reviews* 2001;25(5):427–43. [PubMed: 11566480]
- Savasta M, Dubois A, Scatton B. Autoradiographic localization of DA-1 dopamine receptors in the rat brain with [3H]SCH 23390. *Brain Research* 1986;375(2):291–301. [PubMed: 2942221]
- Serra G, Collu M, D'Aquila PS, De Montis GM, Gessa GL. Possible role of dopamine DA-1 receptor in the behavioural supersensitivity to dopamine agonists induced by chronic treatment with antidepressants. *Brain Research* 1990;527(2):234–43. [PubMed: 1979237]
- Siemiakowski M, Rokicki D, Członkowska AI, Sienkiewicz-Jarosz H, Bidziński A, Płażnik A. Locomotor activity and a conditioned fear response: correlation with cortical and subcortical binding of the dopamine DA-1 receptor antagonist. *Neuroreport* 2000;11(18):3953–6. [PubMed: 11192608]
- Sotak BN, Hnasko TS, Robinson S, Kremer EJ, Palmiter RD. Dysregulation of dopamine signaling in the dorsal striatum inhibits feeding. *Brain Research* 2005;1061(2):88–96. [PubMed: 16226228]
- Steimer T, Driscoll P. Divergent stress responses and coping styles in psychogenetically selected Roman high-(RHA) and low-(RLA) avoidance rats: behavioural, neuroendocrine and developmental aspects. *Stress* 2003;6(2):87–100. [PubMed: 12775328]
- Steimer T, Python A, Schulz PE, Aubry JM. Plasma corticosterone, dexamethasone (DEX) suppression and DEX/CRH tests in a rat model of genetic vulnerability to depression. *Psychoneuroendocrinology* 2007;32(5):575–9. [PubMed: 17512120]
- Svenningsson P, Nishi A, Fisone G, Girault JA, Nairn AC, Greengard P. DARPP-32: an integrator of neurotransmission. *Annual Review of Pharmacology and Toxicology* 2004;44:269–96.

- Takamori K, Yoshida S, Okuyama S. Repeated treatment with imipramine, fluvoxamine and tranylcypromine decreases the number of escape failures by activating dopaminergic systems in a rat learned helplessness test. *Life Sciences* 2001;69(16):1919–26. [PubMed: 11693272]
- Taoka H, Hamamura T, Endo S, Miki M, Lee Y, Miyata S, Toma K, Ishihara T, Sagara H, Gomita Y, Kuroda S. G(olf) protein levels in rat striatum are increased by chronic antidepressant administration and decreased by olfactory bulbectomy. *Life Sciences* 2006;79(5):462–8. [PubMed: 16546220]
- Tejani-Butt SM, Paré WP, Yang J. Effect of repeated novel stressors on depressive behavior and brain norepinephrine receptor system in Sprague-Dawley and Wistar Kyoto (WKY) rats. *Brain Research* 1994;649(1–2):27–35. [PubMed: 7953642]
- Tejani-Butt S, Kluczynski J, Paré WP. Strain-dependent modification of behavior following antidepressant treatment. *Progress in Neuropsychopharmacology and Biological Psychiatry* 2003;27(1):7–14.
- Trevitt JT, Carlson BB, Nowend K, Salamone JD. Substantia nigra pars reticulata is a highly potent site of action for the behavioral effects of the D1 antagonist SCH 23390 in the rat. *Psychopharmacology (Berl)* 2001;156(1):32–41. [PubMed: 11465631]
- Trevitt T, Carlson B, Correa M, Keene A, Morales M, Salamone JD. Interactions between dopamine D1 receptors and gamma-aminobutyric acid mechanisms in substantia nigra pars reticulata of the rat: neurochemical and behavioral studies. *Psychopharmacology (Berl)* 2002;159(3):229–37. [PubMed: 11862355]
- Yaroslavsky I, Colletti M, Jiao X, Tejani-Butt S. Strain differences in the distribution of dopamine (DA-2 and DA-3) receptor sites in rat brain. *Life Sciences* 2006;79(8):772–6. [PubMed: 16574158]
- Zamudio S, Fregoso T, Miranda A, De La Cruz F, Flores G. Strain differences of dopamine receptor levels and dopamine related behaviors in rats. *Brain Research Bulletin* 2005;65(4):339–47.

Fig. 1.
The binding of [^3H] - SCH23390 to D1 receptor sites in the CPu of WKY and Wistar rats. Data are expressed as the mean $\pm$ S.E.M. of measurements from 6 rats from each strain with determinations made in duplicate sections from each brain. * Represents significant differences (Student's *t*-test, $p < 0.05$) between the two strains.

Fig. 2.
The binding of [^3H] - SCH23390 to D1 receptor sites in the NAc shell and core of WKY and Wistar rats. Data are expressed as the mean $\pm$ S.E.M. of measurements from 6 rats from each strain with determinations made in duplicate sections from each brain. * Represents significant differences (Student's *t*-test, $p < 0.05$) between the two strains.

Fig. 3.
The binding of [^3H] - SCH23390 to D1 receptor site in the SNr of WKY and Wistar rats. Data are expressed as the mean $\pm$ S.E.M. of measurements from 6 rats from each strain with determinations made in duplicate sections from each brain. * Represents significant differences (Student's *t*-test, $p < 0.05$) between the two strains.

Fig. 4. Representative autoradiograms of Plate 12 (A and B) and Plate 42 (B and C) (Paxinos and Watson, 1998) showing total $[^3\text{H}]\text{-SCH23390}$ binding to DA-1 receptors in a WKY (left) and WIS rat (right).