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The quetiapine active metabolite N-Desalkylquetiapine and the neurotensin NTS1 receptor agonist PD149163 exhibit antidepressant-like effects on operant responding in male rats

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Running Head: Antidepressant effects of N-Desalkylquetiapine and PD149163

The quetiapine active metabolite N-Desalkylquetiapine and the neurotensin NTS_1 receptor agonist PD149163 exhibit antidepressant-like effects on operant responding in male rats

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Todd M. Hillhouse is now at the University of Michigan in the Department of Pharmacology. Katelin S. Matazel is now at the Food and Drug Administration, National Center for Toxicological Research. Ashley A. Keiser is now at the University of Michigan in the Department of Psychology.

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Abstract

Major depressive disorder (MDD) is the most common mood disorder in the United States and European Union; however, the limitations of clinically available antidepressant drugs have led researchers to pursue novel pharmacological treatments. Clinical studies have reported that monotherapy with the atypical antipsychotic drug quetiapine produces a rapid reduction in depressive symptoms that are apparent following one week of quetiapine treatment, and it is possible that the active metabolite N-Desalkylquetiapine, which structurally resembles an antidepressant drug, produces antidepressant effects. Neuropharmacological evaluations of the neurotensin NTS_1 receptor agonist PD149163 are suggestive of antidepressant efficacy, but the effects of a NTS_1 receptor agonist in an antidepressant animal model have yet to be reported. The present study examined the antidepressant-like effects of the N-Desalkylquetiapine, the neurotensin NTS_1 receptor agonist PD14916, quetiapine, the tricylic antidepressant drug imipramine, the atypical antipsychotic drug risperidone, and the typical antipsychotic drug raclopride on responding in male Sprague-Dawley rats trained on a differential-reinforcement-of-low-rate (DRL) 72 s operant schedule, a procedure used for screening antidepressant drugs. Quetiapine, PD149163, risperidone, and imipramine exhibited antidepressant-like effects by increasing the number of reinforcers earned, decreasing the number of responses emitted, and shifting the interresponse time (IRT) distributions to the right. N-Desalkylquetiapine produced a partial antidepressant-like effect by decreasing the number of responses emitted and producing a rightward shift in the IRT distributions, but it did not significantly alter the number of reinforcers earned. The typical antipsychotic drug raclopride decreased both reinforcers and responses. These data suggest that N-Desalklyquetiapine likely contributes to quetiapine's antidepressant

efficacy and identifies NTS_1 receptor activation as a potential novel pharmacologic strategy for antidepressant drugs.

Keywords: N-Desalklyquetiapine; PD149613; Quetiapine; differential-reinforcement-of-low-rate (DRL); neurotensin; depression

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The quetiapine active metabolite N-Desalkylquetiapine and the neurotensin NTS_1 receptor agonist PD149163 exhibit antidepressant-like effects on operant responding in male rats

Major depressive disorder (MDD) is a recurring and debilitating mental disorder with a lifetime prevalence of 14.4% in the United States (Kessler, Petukhova, Sampson, Zaslavsky & Wittchen, 2012). Clinicians have several types pharmacological treatments available for MDD, which include newer (i.e. selective-serotonin reuptake inhibitors [SSRI] and serotonin-norepinephrine reuptake inhibitors [SNRI]), older (i.e. tricyclic antidepressants [TCA] and monoamine oxidase inhibitors [MAOI]), and atypical (e.g., bupropion and vortioxetine) antidepressant medications. However, only about one-half of patients achieve a significant attenuation of symptoms, although not complete symptom remission. Moreover, the delayed onset for an attenuation of symptoms remains a concern for clinically available antidepressant drugs (Fava & Davidson, 1996; Rush et al., 2006; Schulberg, Katon, Simon, & Rush, 1998). Novel strategies for antidepressant drugs include glutamatergic antagonists, such as ketamine (Murrough et al., 2013; Zarate et al., 2006), monotherapy with certain atypical antipsychotic drugs, such as quetiapine (Bortnick et al., 2011; Cutler et al., 2009), and endogenous substances that may broadly alter monoaminergic neurotransmission, such as the neuropeptide neurotensin.

The atypical antipsychotic drug quetiapine XR (quetiapine fumarate extended release tablets) has been approved by the United States Food and Drug Administration (FDA) as an adjunctive treatment to antidepressants for MDD patients with inadequate response to antidepressant treatment alone. Additionally, quetiapine has shown promise as monotherapy for the treatment of MDD in both clinical and preclinical studies. For example, several clinical studies have shown that once-daily quetiapine XR (50-300 mg/d) produces a rapid reduction in

depressive symptoms after one week of treatment and continues to reduce depressive symptoms for six to eight weeks (i.e. the completion of the study) (Bortnick et al., 2011; Cutler et al., 2009; Weisler et al., 2009). In animals, quetiapine produces antidepressant-like effects in the forced swim test and in behavioral tests following a period of chronic mild stress (Kotagale, Mendhi, Aglawe, Umekar, & Taksande, 2013; Orsetti et al., 2007; Orsetti, Brisco, Rinaldi, Dallorto, & Ghi, 2009).

Quetiapine has a diverse pharmacological binding profile with high affinities for histamine (H_1) receptors and adrenergic (α_{1A}, α_{1B}, α_{2C}) adrenoceptors, and moderate affinities for serotonin (5-HT_{1A}, 5-HT_{2A}, 5-HT_7) and dopamine (D_2) receptors (Jensen et al., 2008; Kroeze et al., 2003; Lopez-Munoz & Alamo, 2013). The active metabolite of quetiapine, N-desalkylquetiapine, which structurally resembles the tetracyclic antidepressant drugs amoxapine and the TCA desipramine, likely contributes to the antidepressant effects of quetiapine and has high affinities for norepinephrine transporters (NET) and serotonergic (5-HT_{1A}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_7), histaminergic (H_1), and muscarinic (M_1, M_3, M_5) receptors (Jensen et al., 2008). Moreover, N-desalkylquetiapine has reduced immobility in a tail-suspension test without increasing locomotor activity in an open field in mice, and these effects are representative of clinically-effective antidepressant drugs in animal models (Jensen et al., 2008).

Neurotensin is a widely distributed neuropeptide neurotransmitter that is synthesized and released from dopamine and other neurons and has extensive interactions, primarily via NTS_1 receptors, with monoamine, cholinergic, GABAergic, and glutamatergic neurons (Binder, Kinkead, Owens, & Nemeroff, 2001; St-Gelais, Jomphe, & Trudeau, 2006). These interactions have led to investigations into the potential role of neurotensin in the pathophysiology of central nervous system disorders (St-Gelais et al., 2006) and the evaluation of brain-penetrant

neurotensin receptor agonists for the treatment pain (e.g., Buhler Choi, Proudfit, & Gebhart, 2005), drug dependence (e.g., Fredrickson, Boules, Stennett, & Richelson, 2014), anxiety (Shilling & Feifel, 2008; Prus, Hillhouse, & LaCrosse, 2014), and schizophrenia (e.g., Holly, Ebrecht, & Prus, 2011). Moreover, we previously reported in this journal that the neurotensin NTS_1 receptor agonist PD149163 improves memory in Brown Norway rats, suggesting that activation of NTS_1 receptors may improve cognitive functioning in schizophrenia (Keiser et al. in press).

A growing literature exists on the potential involvement of neurotensin in depression and the utility of neurotensin receptors agonists for treating depression. Neurotensin NTS_1 receptor knockout mice have increased immobility time in the tail suspension test as compared to wild-type controls, which suggests a depression-like phenotype (Fitzpatrick et al., 2012). Direct injection of neurotensin into the ventral tegmental area was shown to decrease immobility in a forced swim test, an indication of antidepressant-like activity (Cervo, Rossi, Tatarczynska, & Samanin, 1992). Brain penetrant NTS_1 receptor agonists also exhibit behavioral effects in animals models mediated by monoamine neurotransmission. For example, central administration of neurotensin (Luttinger et al., 1982) and systemic administration of the NTS_1 receptor agonists PD149163 (Holly et al., 2011) and NT69L (Hertel, Olsen, & Arnt, 2002) reduces conditioned avoidance responding in rats, an effect predictive of clinical antipsychotic efficacy and that is mediated by dopamine D_2 receptor antagonism (Wadenberg & Hicks, 1999). Moreover, systemic administration of the NTS_1 receptor agonist NT69L in rats has been shown to increase dopamine concentrations in the medial prefrontal cortex, which may be mediated, in part, by serotonin 5-HT_{1A} receptors (Prus, Huang, Li, Dai, & Meltzer, 2007).

A further preclinical evaluation of N-Desalkylquetiapine and a NTS_1 receptor agonist would aid in evaluating the potential antidepressant effects of these compounds. A reliable behavioral procedure for screening antidepressant drugs in animals is the differential-reinforcement-of-low-rate (DRL) 72 s operant task. In the DRL 72 s procedure, which requires a rat to withhold operant responding for 72 s in order to earn a reinforcer, antidepressant drugs increase reinforcement rates, decrease response rates, and produce a rightward shift in the interresponse time (IRT) distributions (for review, see O'Donnell, Marek, & Seiden, 2005). For example, imipramine (Tofranil®; TCA), iproniazid (Marsilid®; MAOI), fluoxetine (Prozac®; SSRI), and sertaline (Zoloft®; SSRI) are all antidepressant drugs from different pharmacological classes that produce antidepressant-like effects in the DRL 72 s task (Hillhouse & Porter, 2014; O'Donnell & Seiden, 1982; O'Donnell & Seiden, 1983; Sokolowski & Seiden, 1999). The DRL 72 s operant procedure offers high predictive validity and is used as tool for screening novel antidepressant drugs. For example, the *N*-methyl-D-aspartate (NMDA) antagonist ketamine, which produces rapid and sustained antidepressant effects in MDD patients, exhibits an antidepressant-like profile in the DRL 72 s task (Hillhouse & Porter, 2014).

Thus, the aim of the present study was to assess antidepressant-like effects of the atypical antipsychotic drugs quetiapine, N-Desalkylquetiapine, and the NTS_1 receptor agonist PD149163 using the DRL 72 s task. The atypical antipsychotic drug risperidone, which neither exhibits antidepressant effects nor produces an active metabolite with antidepressant effects, the typical antipsychotic drug and $D_{2/3}$ antagonist raclopride, and the tricyclic antidepressant drug imipramine, which reliably produces an antidepressant-like profile in the DRL 72 s procedure, were assessed for comparison. We hypothesized that quetiapine, N-Desalkylquetiapine, and PD149163 would exhibit antidepressant-like effects in this model, whereas risperidone and

raclopride would not produce antidepressant-like effects based on previous literature (for review, see O'Donnell, Marek, & Seiden, 2005).

Method

Subjects

Twelve adult male Sprague-Dawley rats (Charles River, Portage, MI, USA) weighing between 300 and 350 grams at the start of the experiment were housed individually in plastic cages in a temperature- and humidity-controlled vivarium kept on a 12-h/12-h light/dark cycle (lights on 0700-1900 h). Sprague-Dawley rats were selected because they are commonly used in the DRL 72 s procedure (O'Donnell et al., 2005). All testing and training sessions occurred during the light cycle, which also was selected based upon other DRL 72 s studies (e.g., Hillhouse & Porter, 2014; O'Donnell et al., 2005; O'Donnell & Seiden, 1982). After one week of acclimation to the vivarium, daily access to food was restricted in order to maintain the rats at 85% of their *ad libitum* weights. Rats had free access to water except during experimental sessions. All experimental procedures were approved by the Institutional Animal Care and Use Committee at Northern Michigan University and conducted in accordance with the Guide for the Care and Use of Laboratory Animals (Institute of Laboratory Animals Resources, 2011).

Apparatus

Six identical operant conditioning chambers (29.2 x 30.5 x 24.1 cm) enclosed in sound attenuating cubicles were used for the DRL 72 s experiments (Med-Associates, St. Albans, VT, USA). Each chamber was equipped with a house light, ventilation fan, two retractable levers, and a food pellet dispenser. A house light was mounted on the middle panel of the back wall of each chamber. On the opposite wall, a retractable lever (4.5 cm wide, extended 2.0 cm, 3 cm off the floor) was mounted on the right side of a food trough. The reinforcers were 45 mg purified diet

pellets (Bio-Serv, Frenchtown, NJ, USA). Fans mounted in the sound attenuating cubicles provided background white noise. Programming of behavioral sessions and data collection were computer controlled by Med-State software (Med PC, Version 4.1, Med-Associates) running on a Windows XP operating system.

Drugs

The atypical antipsychotic drug quetiapine (NIMH Drug Repository, Bethesda, MD, USA), the active quetiapine metabolite, N-Desalkylquetiapine (a gift from NeuroDetective International, Wyncote, PA), and the atypical antipsychotic drug risperidone (Sigma-Aldrich, St. Louis, MO) were dissolved in sterile water with the aid of 1-2 drops of 85% lactic acid. The neurotensin NTS_1 receptor agonist PD149163 (gift from the NIHM Drug Repository, Bethesda, MD), the tricyclic antidepressant imipramine (Sigma-Aldrich), and the selective $D_{2/3}$ receptor antagonist raclopride L-tartrate (Sigma-Aldrich) were dissolved in 0.9% physiological saline. All drugs were administered intraperitoneally (i.p.) in a volume of 1 ml/kg, whereas raclopride was administered subcutaneously (s.c.). Drugs, doses, and pretreatment times were as follows: quetiapine (2.5-10.0 mg/kg i.p.; 30 min), N-Desalkylquetiapine (2.5-10.0 mg/kg i.p.; 30 min), PD149163 (0.0312-0.25 mg/kg i.p.; 30 min), risperidone (0.125-0.5 mg/kg i.p.; 30 min), imipramine (2.5-10.0 mg/kg i.p.; 30 min), and raclopride (0.00625-0.05 mg/kg s.c.; 30 min). Drug and dose order across rats was counterbalanced using a Latin-square design to minimize impact of drug history effects. Doses and administration routes were based on previous literature (O'Donnell et al. 2005) and preliminary studies in this laboratory.

Differential-reinforcement-of-low-rate 72 s procedure

All rats were first given one session of magazine training in which the house light was on, but the levers were not extended into the chamber. During magazine training, one reinforcer

(i.e. food pellet) was delivered noncontingently according to a fixed-time 60 s schedule for 30 min. For the remaining training and test sessions the house light was on and the right lever was extended from the wall. During the next three sessions, rats were trained to lever press under a fixed-ratio 1 reinforcement schedule, in which each lever press resulted in delivery of a reinforcer. Sessions ended after delivery of 30 reinforcers or 60 min, whichever occurred first. Following the completion of lever press training, all rats started DRL training.

Under the DRL schedule, a response produced a reinforcer only after a specified interresponse interval had elapsed. Lever presses emitted before expiration of the interresponse interval reset the timer and did not produce a reinforcer. The interresponse interval was gradually increased over 15 training sessions. Specifically, DRL training began with an 18 s interresponse interval for 5 sessions, then was increased to 36 s for 10 sessions, and finally increased to 72 s until DRL performance stabilized. DRL performance was considered stable when the number of responses for each individual rat did not vary by more than 10% over 5 out of 6 consecutive sessions. All DRL training and testing sessions were 60 min in length.

Once stable performance under the terminal DRL schedule (i.e. 72 s) was established, test sessions occurred twice weekly (typically Tuesday and Friday) without training sessions between each test session. After the completion of a dose-effect curve for a given drug, the rats received at least three training sessions at the start of the dose-effect curve for the next drug. If DRL performance remained stable in a given rat after completion of testing with the initial drug, then the rat was advanced to testing with another drug.

Data Analysis

The three dependent variables were 1) total number of reinforcers delivered during each test session, 2) total number of responses during each test session, and 3) inter-response times

(IRT) for all responses during each test session. All data were expressed as means (+/- standard error of the mean [SEM]). Response and reinforcer data were analyzed using a one-way repeated measures analysis of variance (ANOVA), with drug dose as the within subjects factor. IRT distributions were obtained by recording responses in nine 12-s bins. To determine if there was a shift in the IRT distribution, a two-way repeated measures ANOVA was used with drug dose as one within subjects factor and interresponse time as the other within subjects factor. Dunnett's multiple comparisons post hoc tests were conducted, as appropriate. Data were analyzed using GraphPad Prism version 6.0 for Windows (GraphPad Software, San Diego, CA, USA).

Results

Training and baseline performance

Eleven of the 12 rats met the training criterion after a mean of 25.27 (± 3.79 SEM) training sessions. The remaining rat was removed from the study after failing to meet the training criteria within 80 training sessions, which was more than two standard deviations beyond the mean number of sessions to criterion for rats that met the training criteria. A repeated measures ANOVA using "drug vehicle" as the within subjects factor, with the vehicle data for each drug serving as different levels of this factor, did not reveal any significant differences for the number of reinforcers earned or the number of responses emitted over the course of the study (data not shown).

Quetiapine

Figure 1 shows the effects of quetiapine, N-Desalkylquetiapine, and PD149163 on DRL 72 s performance. Quetiapine produced a significant increase in the number of reinforcers obtained, $F(3, 27) = 5.61$, $p = .004$, which occurred at a 5.0 and 10.0 mg/kg dose compared to vehicle (figure 1a). Quetiapine also significantly altered the number of responses emitted, $F(3,$

27) = 3.19, p = .04, with a 10.0 mg/kg dose of quetiapine leading to a reduction in responses compared to vehicle (figure 1b).

For the IRT distribution, quetiapine produced a significant main effect of IRT time bin, $F(8, 72) = 9.47$, $p < .001$; no main effect of dose, $F(3, 27) = 1.28$, $p = .30$; and a significant interaction effect, $F(24, 216) = 2.09$, $p = .003$ (Figure 1c). The 5.0 mg/kg dose of quetiapine significantly decreased the responses emitted in the 48 s time bin and increased responses emitted after 96 s as compared to vehicle, whereas the 10.0 mg/kg dose of quetiapine only increased responses emitted after 96 s as compared to vehicle. Overall, these effects indicate that a rightward shift in the IRT distribution occurred for these doses, compared to vehicle.

N-Desalkylquetiapine

N-Desalkylquetiapine produced a trend toward a statistically significant increase in the number of reinforcers earned, $F(3, 30) = 2.51$, $p = .08$ (Figure 1d). N-Desalkylquetiapine significantly decreased the number of responses emitted, $F(3, 30) = 4.27$, $p = .01$ (Figure 1e), which occurred at a 5.0 and 10.0 mg/kg dose compared to vehicle.

For the IRT distribution, N-Desalkylquetiapine produced a significant main effect of IRT, $F(8, 80) = 15.10$, $p < .001$; no main effect of dose, $F(3, 30) = 0.38$, $p = .77$; and a significant interaction effect, $F(24, 240) = 1.68$, $p = .03$ (Figure 1f). Specifically, the 2.5 mg/kg dose of N-Desalkylquetiapine decreased responses emitted during the 48 s time bin compared to vehicle. The 5.0 mg/kg dose of N-Desalkylquetiapine decreased responses emitted during the 35 s time bin, and both 5.0 and 10.0 mg/kg N-Desalkylquetiapine increased responses emitted during the 72 s time bin compared to vehicle. Overall, these effects indicate that treatment with 5.0 and 10.0 mg/kg N-Desalkylquetiapine produced a modest rightward shift in the IRT distribution compared to vehicle.

PD149163

PD149163 significantly increased the number of reinforcers earned, $F(3, 30) = 5.75$, $p = .003$ (Figure 1g), and significantly decreased the number of responses emitted, $F(3, 30) = 5.50$, $p = .004$ (Figure 1h), which occurred at the 0.0625 and 0.125 mg/kg doses as compared to vehicle.

For the IRT distribution, PD149163 produced a significant main effect of IRT time bin, $F(8, 80) = 7.19$, $p < .001$; no main effect of dose, $F(3, 30) = 0.99$, $p = .41$; and a significant interaction of IRT time bin and drug dose, $F(24, 240) = 3.52$, $p < .001$ (Figure 1i). Treatment with 0.0625 mg/kg PD149163 decreased responses emitted during the 36 s time bin and increased responses emitted after 96 s time bins. The high dose of PD149163 (0.125 mg/kg) decreased responses emitted in the 24 s, 36 s and 48 s time bins and increased responses emitted after 96 s, compared to vehicle. Overall, these effects indicate that treatment with 0.0625 and 0.125 mg/kg PD149163 produced a rightward shift in the IRT distribution compared to vehicle.

Risperidone

Figure 2 shows the effects of risperidone, imipramine, and raclopride on DRL 72 s performance. Risperidone produced a significant effect on number of reinforcers earned, $F(3, 30) = 9.25$, $p < .001$. The 0.25 mg/kg dose increased the number of reinforcers earned, whereas the 0.5 mg/kg dose did not alter the number of reinforcers earned, compared to vehicle (Figure 2a). Risperidone significantly decreased the number of responses emitted during the test session, $F(3, 30) = 7.69$, $p < .001$ (Figure 2b), which occurred at a 0.25 and 0.5 mg/kg dose of risperidone compared to vehicle.

For the IRT distribution, risperidone produced a significant main effect of IRT time bin, $F(8, 80) = 8.25$, $p < .001$; no main effect of dose, $F(3, 30) = 1.85$, $p = .16$; and a significant interaction of IRT time bin and drug dose, $F(24, 240) = 2.21$, $p = .001$ (Figure 2c). The 0.25

mg/kg dose of risperidone decreased responses emitted in the 48 s time bin and increased responses emitted in the 84 s and after 96 s time bins compared to vehicle. Additionally, 0.5 mg/kg risperidone only increased responses emitted after 96 s as compared to vehicle. Overall, these results indicate that 0.25 mg/kg risperidone produced a rightward shift in the IRT distribution compared to vehicle.

Imipramine

Imipramine significantly increased the number of reinforcers earned, $F(3, 30) = 8.13$, $p < .001$ (Figure 2d), which occurred at the 5.0 and 10.0 mg/kg doses of imipramine compared to vehicle. Relative to vehicle, all doses of imipramine (2.5-10.0 mg/kg) significantly decreased the number of responses emitted, $F(3, 30) = 6.89$, $p = .001$ (Figure 2e).

For the IRT distribution, imipramine produced a significant main effect of IRT time bin, $F(8, 80) = 9.08$, $p < .001$; no main effect of dose, $F(3, 30) = 1.15$ $p = .35$; and a significant interaction of IRT time bin and drug dose, $F(24, 240) = 3.96$, $p < .001$ (Figure 2f). Specifically, the 2.5 mg/kg imipramine dose decreased the number of responses emitted in the 24 s and 36 s time bins and increased responses in the 72 s time bin compared to vehicle. The 5.0 mg/kg dose of imipramine failed to significantly alter the IRT distribution compared to vehicle, while the high dose of imipramine (10.0 mg/kg) only increased the number of responses after 96 s as compared to vehicle. Overall, these result indicate that a 2.5 mg/kg dose of imipramine produced a rightward shift in the IRT distribution compared to vehicle.

Raclopride

Raclopride significantly decreased the number of reinforcers earned during test sessions, $F(4, 40) = 6.50$, $p < .001$ (Figure 2g), and significantly decreased the number of responses emitted, $F(4, 40) = 27.28$, $p < .001$ (Figure 2h). The 0.025 mg/kg dose decreased only responses,

whereas the 0.05 mg/kg dose decreased both reinforcers and responses. For the IRT distribution, raclopride produced a significant main effect of IRT time bin, $F_{(8, 80)} = 8.34$, $p < .001$, significant main effect of dose, $F_{(4, 40)} = 3.61$ $p = .01$, and a significant interaction of IRT time bin and drug dose, $F_{(32, 320)} = 6.08$, $p < .001$ (Figure 2i). Specifically, treatment with 0.025 and 0.05 mg/kg raclopride decreased responses emitted in the 48 s and 60 s time bins and increased responses emitted after 96 s as compared to vehicle.

Discussion

The present study found that quetiapine, PD149163, risperidone, and imipramine produced antidepressant-like effects using a DRL 72 s task as shown by an increase in reinforcers, a decrease in responses, and a rightward shift in the IRT distributions. This is the first study to report an antidepressant effect generated by an NTS_1 receptor agonist. N-Desalkylquetiapine produced a partial antidepressant-like effect by decreasing responses and producing a rightward shift in the IRT distributions, and provided a trend toward a significant increase in the number of reinforcers earned ($p = 0.08$). Conversely, raclopride decreased both the number of reinforcers and responses and flattened the IRT distributions, which is an effect consistent with other D_2 receptor antagonists tested in the DRL 72 s task (O'Donnell, Marek, & Seiden, 2005).

The antidepressant-like effects produced by quetiapine, PD149163, and risperidone are consistent with TCAs (e.g. imipramine and amitriptyline), MAOIs (e.g. tranylcypromine, iproniazid, and isocarboxazid), SSRIs (e.g. fluoxetine and sertraline), and atypical antipsychotics (e.g. clozapine), which also increase reinforcement rate, decrease response rate and shift the IRT distributions to the right (Hillhouse & Porter, 2014; Howard & Pollard, 1984; O'Donnell & Seiden, 1982; O'Donnell & Seiden, 1983; Sokolowski & Seiden, 1999). In contrast, the typical

antipsychotic drugs haloperidol and raclopride have been shown to decrease both reinforcers and responses (Jackson, Koek, & Colpaert, 1995; Seiden, Dahms, & Shaughnessy, 1985; and in the present study), indicating a lack of antidepressant effects using the DRL 72 s task.

The antidepressant-like effects of quetiapine in the present study supports previous preclinical and clinical reports suggesting that monotherapy with quetiapine produces antidepressant effects. For example, acute administration of quetiapine produces an antidepressant-like effect in mice subjected to the forced swim test by decreasing the time spent immobile (Kotagale et al., 2013). Additionally, rats treated with chronic administration of quetiapine exhibited an anhedonic reduction in sucrose preference that was shown in non-quetiapine treated rats after acute swim stress and 6 weeks exposure to chronic mild stressors (Orsetti et al., 2007; Orsetti et al., 2009). Furthermore, quetiapine XR produces antidepressant effects following acute (one week) and chronic (6 to 8 weeks) treatment in adults and elderly MDD patients (Bortnick et al., 2011; Cutler et al., 2009; Katila et al., 2013; Weisler et al., 2009).

N-Desalkylquetiapine produced partial antidepressant-like effects in that N-Desalkylquetiapine decreased the number of responses and produced a rightward shift in the IRT distributions but did not increase the number of reinforcers earned (although there was a trend towards significant $p = .08$). N-Desalkylquetiapine is a potent NET inhibitor and partial 5-HT_{1A} agonist and it has a chemical structure similar to the tetracylic antidepressant drug desipramine (Jensen et al., 2008). Compounds comparable to this profile, such as the NET inhibitor reboxetine and typical antipsychotic drug and tricyclic phenothiazine chlorpromazine, also decreased response rates and shifted IRT distributions to the right without significantly increasing reinforcement rate in this task (Dekeyne, Gobert, Auclair, Girardon, & Millan, 2002; O'Donnell & Seiden, 1983). N-Desalkylquetiapine has also demonstrated an antidepressant

effect in a forced swim task in mice (Jensen et al., 2008). Moreover, a reduction in depressive symptoms among bipolar disorder patients has been shown to correlate with increased N-Desalkylquetiapine/quetiapine plasma ratios (Altamura et al., 2012). Taken together, the present and earlier findings support the role of an active metabolite contributing to quetiapine's antidepressant effects.

This was the first study to report an antidepressant-like effect by a neurotensin receptor agonist. PD149163 exhibits a high affinity for the neurotensin NTS_1 receptor and is devoid of activity at monoaminergic, cholinergic, GABAergic, or glutamatergic neurotransmitter receptors (Petrie et al. 2004), although PD149163 and other NTS_1 receptor agonists exhibit a panoply of effects on other neurotransmitter systems. NTS_1 receptors are postsynaptically localized in the ventral tegmental area, basal ganglia, nucleus accumbens, nucleus basalis magnocellularis, and dorsal raphe nuclei (Jolas & Aghajanian, 1997; Binder et al., 2001; St-Galais et al., 2006). Intracerebroventricular administration of neurotensin has been shown to increase 5-HT turnover in the nucleus accumbens and decrease 5-HT turnover in the ventral tegmental area (Drumheller, Gagne, St-Pierre, & Jolicoeur, 1990). Activation of postsynaptic NTS_1 receptors in the raphe nuclei depolarizes serotonin neurons (Li, Yeh, Tan, Hwang, & Wang, 2001) and facilitates serotonin release in the prefrontal cortex (Petkova-Kirova et al., 2008). NTS_1 receptors have close interactions with dopamine, including presynaptic localization of NTS_1 receptors on dopamine terminals in the prefrontal cortex and nucleus accumbens. On dopamine terminals, activation of NTS_1 receptors inhibit dopamine D_2 autoreceptor function, leading to a disinhibition of dopamine efflux (Binder et al., 2001). Given recent studies describing NTS_1 receptor stimulation as a potential treatment for nicotine (Boules et al., 2011) and the ability of these agonist to increase dopamine concentrations in the nucleus accumbens (Sotty et al., 2000;

Prus et al., 2007) there is some potential for these compounds to reduce anhedonia in depression by elevating dopamine concentrations in the nucleus accumbens (Treadway & Zald, 2011).

While previous literature has not shown risperidone to exhibit antidepressant effects in a DRL 72 s procedure (O'Donnell et al., 2005), risperidone exhibited antidepressant-like effects in the present study. In several clinical case-studies, adjunctive treatment with risperidone has been shown to produce rapid (ranging from one day to two weeks) antidepressant effects and reduce suicidality (O'Connor & Silver, 1998; Ostroff & Nelson, 1999; Stoll & Haura, 2000). Reeve et al. (2008) extended these findings with a double-blind, placebo-controlled study in which adjunctive risperidone treatment (0.25-2.0 mg/day) reduced both depressive symptoms and suicidality within four days and with effects maintained for the duration of the 8 week study. Several preclinical studies have shown that adjunctive risperidone treatment with SSRIs and selective serotonin norepinephrine reuptake inhibitors (SNRIs) produces antidepressant-like effects by decreasing the time spent immobile in the forced swim test in mice (Dhir & Kulkarni, 2008) and rats (Iijima, Kurosu, & Chaki, 2010). In the present study, administration of risperidone produced antidepressant-like effects in the DRL 72 s task, and in previous studies, risperidone has been shown to restore sucrose preference to control levels in rats exposed to seven weeks of chronic mild stress (Marston et al., 2011) and to decrease time spent immobile in pituitary adenylate cyclase-activating polypeptide (PACAP) knockout mice (Hashimoto et al., 2009).

With the exception of PD149163, the compounds tested in the present study all function as antagonists for the 5-HT_{2A} receptor (Jensen et al., 2008; Schotte et al., 1996). Like these compounds, the serotonin 5-HT_{2A} receptor antagonists ketanserin and ritanserin have produced antidepressant-like effects in the DRL 72 s task (Marek, Li, & Seiden, 1989; Marek & Seiden,

1988). Further, preclinical research has shown that neuroadaptive changes occur for 5-HT_{2A} receptors following behavioral stress procedures and chronic antidepressant treatment. For example, an upregulation of 5-HT_{2A} receptors was shown to occur following isolation rearing in mice and chronic mild stress exposure in rats, but not in animals given repeated administration with citalopram and imipramine, respectively (Günther, Liebscher, Jähkel, & Oehler, 2008; Papp, Klimek, & Willner, 1994). Additionally, chronic antidepressant treatment has produced a downregulation of 5-HT_{2A} receptors in rat cortex (Papp et al., 1994; Kendall & Nahorski, 1985; Lafaille, Welner, & Suranyi-Cadotte, 1991; Paul et al., 1988; Peroutka & Snyder, 1980; Todd, McManus, & Baker, 1995). It is possible that antagonism of 5-HT_{2A} receptors produced by the compounds in the present study and in previous studies exhibit an effect pharmacologically similar to effects engendered by downregulation of 5-HT_{2A} receptors, and which may account for the reduced time of onset for antidepressant effects by adjunctive atypical antipsychotic drugs found clinically (Bortnick et al., 2011; Cutler et al., 2009; Katila et al., 2013; Ostroff & Nelson, 1999; Reeve et al., 2008; Weisler et al., 2009).

Conclusion

This study provided an evaluation of the antidepressant effects of two novel and pharmacologically different compounds, N-Desalkylquetiapine and PD149163. The behavioral findings with N-Desalkylquetiapine add to previous data from preclinical and clinical studies suggesting that this compound engenders antidepressant effects. The present study was the first to evaluate systemic administration of a NTS_1 receptor agonist in an antidepressant screening model and revealed that PD149163 engendered, through a very different pharmacological mechanism, effects similar to clinically available antidepressant drugs. Further investigation is needed to determine if neurotensin NTS_1 receptor agonists may produce antidepressant effects in

other models, as well as to determine if tolerance may occur to these effects after chronic administration. Additional supporting evidence for antidepressant efficacy may establish NTS_1 receptor agonism as a novel pharmacologic strategy for antidepressant drug development.

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FIGURE CAPTIONS

Figure 1. Effects of quetiapine (n = 10), N-Desalkylquetiapine (n = 11), and PD149163 (n = 11) on DRL 72 s performance in male Sprague-Dawley rats. Left panels (a, d, g) show drug effects on number of reinforcers earned (Abscissae: drug dose [mg/kg]; Ordinates: number of reinforcers). Center panels (b, e, h) show drug effects on number of responses emitted (Abscissae: drug dose [mg/kg]; Ordinates: number of responses). Right panels (c, f, i) show drug effects on interresponse time (IRT) distributions (Abscissae: IRT duration [12 s bin]; Ordinates: relative frequency of responses). Drug doses are indicated in legends. Filled points represent time bin relative frequencies after drug treatment that were significantly different from vehicle as determined by two-way ANOVA followed by a Dunnett's post hoc test. All data were expressed as means ± S.E.M. $*p < 0.05$ and $**p < 0.01$ for statistically significant differences compared to vehicle.

Figure 2. Effects of risperidone (n = 11), imipramine (n = 11), and raclopride (n = 11) on DRL 72 s performance in male Sprague-Dawley rats. Left panels (a, d, g) show drug effects on number of reinforcers earned. Center panels (b, e, h) show drug effects on number of responses emitted. Right panels (c, f, i) show drug effects on interresponse time (IRT) distributions. Filled points represent time bin relative frequencies after drug treatment that were significantly different from vehicle as determined by two-way ANOVA followed by a Dunnett's post hoc test. All data were expressed as means ± S.E.M. $*p < 0.05$ and $**p < 0.01$ for statistically significant differences compared to vehicle. See figure 1 for other details.

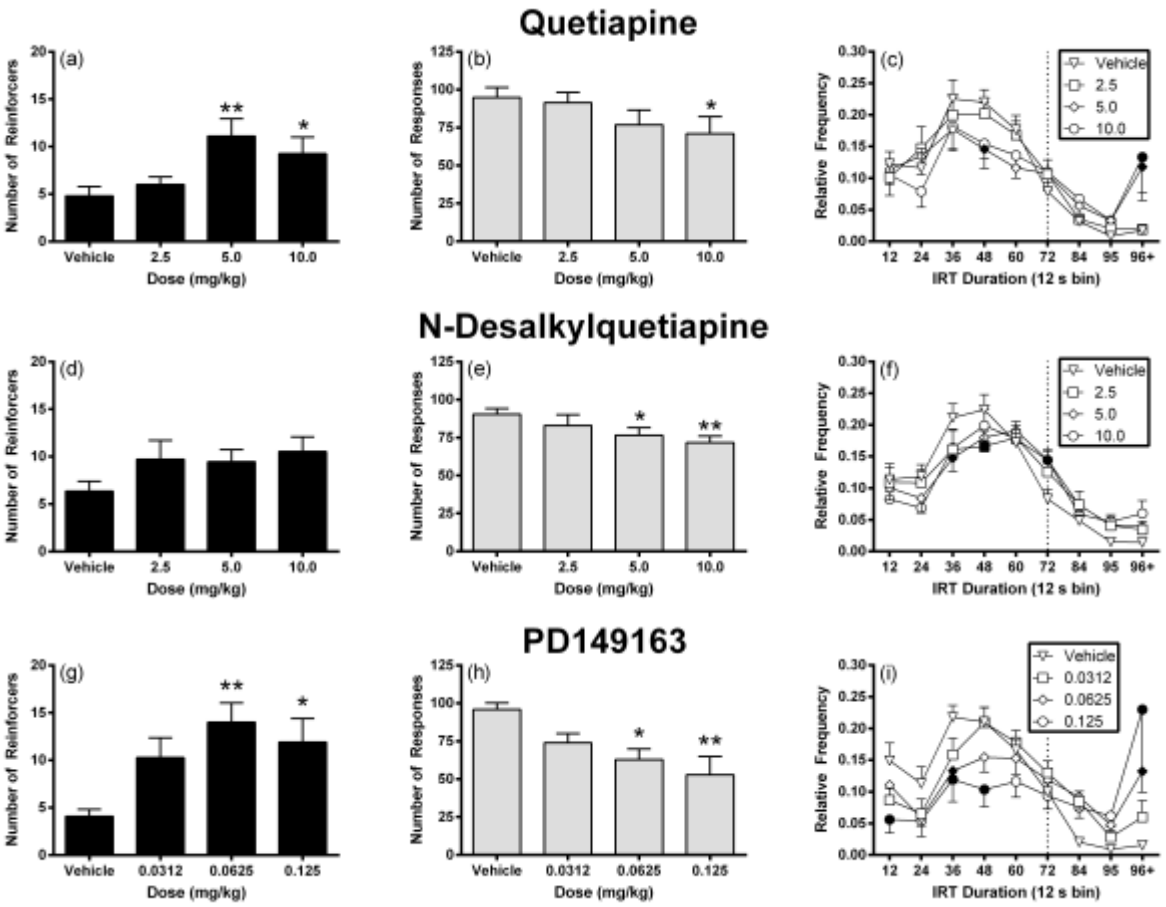
Quetiapine
N-Desalkylquetiapine
PD149163
(a)
(b)
(c)
(d)
(e)
(f)
(g)
(h)
(i)
Number of Reinforcers
Number of Responses
Relative Frequency
Dose (mg/kg)
IRT Duration (12 s bin)
Vehicle
2.5
5.0
10.0
0.0312
0.0625
0.125
12 24 36 48 60 72 84 95 96+

Figure 1.

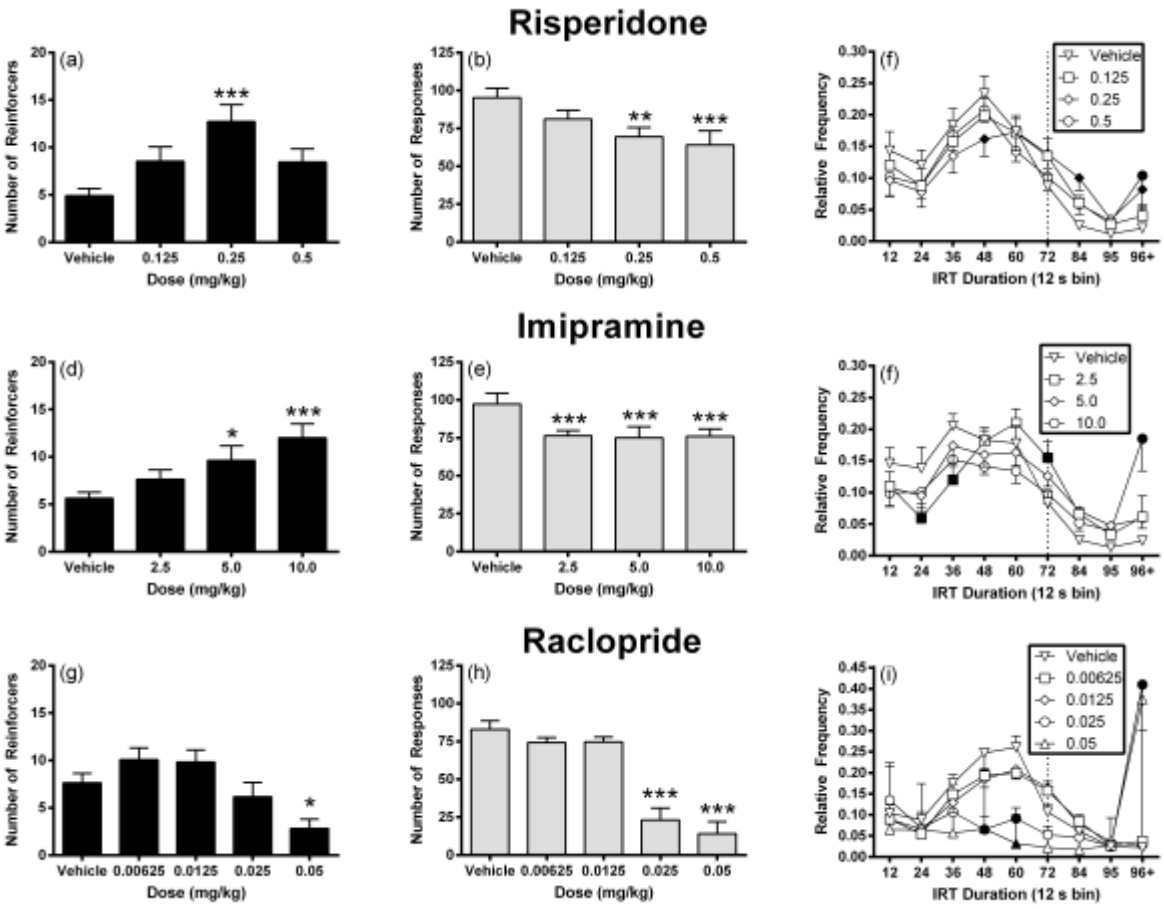
Risperidone
(a)
Number of Reinforcers
Vehicle 0.125 0.25 0.5
Dose (mg/kg)
(b)
Number of Responses
Vehicle 0.125 0.25 0.5
Dose (mg/kg)
(f)
Relative Frequency
Vehicle
0.125
0.25
0.5
12 24 36 48 60 72 84 95 96+
IRT Duration (12 s bin)
Imipramine
(d)
Number of Reinforcers
Vehicle 2.5 5.0 10.0
Dose (mg/kg)
(e)
Number of Responses
Vehicle 2.5 5.0 10.0
Dose (mg/kg)
(f)
Relative Frequency
Vehicle
2.5
5.0
10.0
12 24 36 48 60 72 84 95 96+
IRT Duration (12 s bin)
Raclopride
(g)
Number of Reinforcers
Vehicle 0.00625 0.0125 0.025 0.05
Dose (mg/kg)
(h)
Number of Responses
Vehicle 0.00625 0.0125 0.025 0.05
Dose (mg/kg)
(i)
Relative Frequency
Vehicle
0.00625
0.0125
0.025
0.05
12 24 36 48 60 72 84 95 96+
IRT Duration (12 s bin)

Figure 2.