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Abstract

Background: Many patients suffering from depressive disorders are refractory to treatment with currently available antidepressant medications, while many more exhibit only a partial response. These factors drive research to discover new pharmacological approaches to treat depression. Numerous studies demonstrate evidence of inflammation and elevated oxidative stress in major depression. Recently, major depression has been shown to be associated with elevated levels of DNA oxidation in brain cells, accompanied by increased gene expression of the nuclear base excision repair enzyme, poly(ADP-ribose) polymerase-1. Given these findings and evidence that drugs that inhibit poly(ADP-ribose) polymerase-1 activity have antiinflammatory and neuroprotective properties, the present study was undertaken to examine the potential antidepressant properties of poly(ADP-ribose) polymerase inhibitors.

Methods: Two rodent models, the Porsolt swim test and repeated exposure to psychological stressors, were used to test the poly(ADP-ribose) polymerase inhibitor, 3-aminobenzamide, for potential antidepressant activity. Another poly(ADP-ribose) polymerase inhibitor, 5-aminoisoquinolinone, was also tested.

Results: Poly(ADP-ribose) polymerase inhibitors produced antidepressant-like effects in the Porsolt swim test, decreasing immobility time, and increasing latency to immobility, similar to the effects of fluoxetine. In addition, 3-aminobenzamide treatment increased sucrose preference and social interaction times relative to vehicle-treated control rats following repeated exposure to combined social defeat and unpredictable stress, mediating effects similar to fluoxetine treatment.

Conclusions: The poly(ADP-ribose) polymerase inhibitors 3-aminobenzamide and 5-aminoisoquinolinone exhibit antidepressant-like activity in 2 rodent stress models and uncover poly(ADP-ribose) polymerase as a unique molecular target for the potential development of a novel class of antidepressants.

Keywords: major depression, antidepressant, PARP inhibitor

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Significance Statement

Currently available drugs for the treatment of depression have numerous limitations. Many depressed people do not respond to these drugs, and even more people experience only a partial response. There is a crucial need to find more effective and safe treatments for depression. The novel discovery of a class of drugs with antidepressant properties is described herein using standard animal models used to screen drugs for antidepressant activity. The biological properties of these drugs, called PARP inhibitors, is very different from existing antidepressants. Evidence also demonstrates that these drugs can boost the antidepressant-like effect of a traditional antidepressant.

Introduction

Conditions of elevated oxidative stress and inflammation are proposed to play a role in the pathophysiology of major depressive disorder (MDD) as well as several psychiatric, neurological, and medical diseases (Van Gaal et al., 2006; Maes et al., 2011; Haroon et al., 2012; Leza et al., 2015; Miller et al., 2016; Swardfager et al., 2016). Since oxidative stress can drive inflammation and vice versa, it is likely that these 2 pathophysiological features of MDD are interrelated. Evidence of oxidative stress conditions in MDD include numerous demonstrations in MDD patients of reduced plasma concentrations of free radical scavengers and elevated levels of oxidation products, including oxidized or damaged DNA (Forlenza and Miller, n.d.; Bilici et al., 2001; Owen et al., 2005; Simon et al., 2006; Yager et al., 2010; Maes et al., 2011). Likewise, numerous researchers have reported elevated indices of inflammation in MDD, including C-reactive protein, cytokines, and IgG antibodies (Howren et al., 2009; Maes et al., 2011; Haapakoski et al., 2015). These findings raise the possibility that drugs that prevent inflammation and/or oxidative damage may have antidepressant efficacy (Anderson and Maes, 2014; Miller et al., 2016).

Recently, elevated levels of nucleic acid oxidation have been observed in brain white matter (Szebeni et al., 2016) and the hippocampus (Che et al., 2010) from MDD brain donors compared with normal control brain donors. Both white matter and the hippocampus contain cells that are uniquely susceptible to oxidative stress. In the hippocampus, these cells include CA1 pyramidal neurons (Wang and Michaelis, 2010). In white matter, myelinating oligodendrocytes are the predominant cellular residents, and these cells are normally susceptible to oxidative damage because of their high rate of metabolism, high levels of iron, and relatively low levels of antioxidant enzyme expression (Kim and Kim, 1991; Connor and Menzies, 1996; Thorburne and Juurlink, 1996; Juurlink et al., 1998). Other indicators of oxidative damage to brain white matter in MDD include shortened telomeres, reduced gene expression of antioxidant enzymes, and upregulation of the gene expression of DNA base excision repair enzymes, poly(ADP-ribose) polymerase-1 (PARP1) and oxoguanine glycosylase, in white matter oligodendrocytes from MDD donors (Szebeni et al., 2014, 2016). Interruption of the damaging effects of oxidation in white matter or other susceptible brain regions has the potential to provide therapeutic benefit in the treatment of MDD.

The observation of upregulated PARP1 gene expression in MDD (Szebeni et al., 2016) is particularly interesting given the role of this enzyme in numerous cellular functions. The activity of PARP1 is activated by strand breaks in DNA such as result from oxidative attack of DNA bases. PARP1 uses NAD^+ as a substrate to attach poly(ADP-ribose) (PAR) polymers to proteins, including PARP1 itself and other nuclear proteins, including histones (De Vos et al., 2012). Through PARylation and also protein-protein interactions, PARP1 participates in several molecular pathways, including DNA repair, chromatin remodeling, and activation of NF-κB (Gibson and Kraus, 2012). Drugs that inhibit PARP1 activity have therapeutic benefit in the treatment of certain cancers, because they increase the lethality of DNA damaging anti-cancer treatments (De Vos et al., 2012). Interestingly, PARP inhibition or PARP1 knockout delivers antiinflammatory and/or neuroprotective effects in a variety of experimental disease conditions, including chronic asthma (Zaffini et al., 2016), myocardial infarction (Wayman et al., 2001), stress-evoked immuno-compromise (Drazen et al., 2001), traumatic brain injury (Besson et al., 2003), and cerebral ischemia (Gerace et al., 2012). The finding of elevated DNA oxidation and upregulation of gene expression of PARP1 in white matter in MDD (Szebeni et al., 2016) raises the possibility that pharmacological inhibition of PARP1 could interfere with pathological processes that contribute to this disorder. In light of this possibility, we (Szebeni et al., 2016) and others (Liu et al., 1996; Sigwalt et al., 2011) have demonstrated elevated levels of DNA oxidation in rat brain following repeated exposure to stress, showing that stressed rats may be useful for the study of the behavioral effects of drugs that reverse downstream effects of oxidative damage to brain cells. Since DNA oxidation activates PARP1, which activates NF-κB and downstream inflammation, it seems reasonable to predict that PARP inhibitors may have antidepressant properties that are detectable in rodent stress models.

The possibility that PARP inhibitors could have therapeutic utility in the treatment of MDD is strongly supported by a number of related studies that have not made the direct connection between PARP inhibition and antidepressant action. Though chiefly prescribed as an antibiotic, numerous studies have shown that minocycline mediates a beneficial neuroprotective effect with efficacy for a wide variety of diseases (Chen et al., 2000; Tikka and Koistinaho, 2001; Nirmalananthan and Greensmith, 2005). Interestingly, minocycline is a high affinity inhibitor of PARP-1; subsequent comparison across several tetracycline derivatives found a strong correlation between PARP-1 binding and neuroprotective potency (Alano et al., 2006). Furthermore, antidepressant effects of minocycline have been anecdotally observed in humans as well as in many studies using rodent models (Molina-Hernández et al., 2008; O'Connor et al., 2009; Arakawa et al., 2012; Saeedi Saravi et al., 2016). In a study of inflammation and its behavioral consequences, treatment of rats with the PARP inhibitor 3-aminobenzamide (3-AB) reversed depressive effects caused by lipopolysaccharide injection (Sriram et al., 2015). However, this sickness-based model for depression arguably remains etiologically distant from causes of MDD in humans (Stepanichev et al., 2014).

In the present study, we tested the hypothesis that PARP inhibition will have antidepressant activity using 2 different rodent models involving psychological stress: (1) a combined repeated social defeat and repeated unpredictable stress model, both models of which are used to identify antidepressant effects (O'Leary and Cryan, 2013) and/or used to explore the biological effects of psychological stress in relation to posttraumatic

stress disorder (Whitaker et al., 2014; Borghans and Homberg, 2015); and (2) the Porsolt swim test, commonly used to identify antidepressant/antianxiety drugs (O'Leary and Cryan, 2013). Two structurally different PARP inhibitors were tested: 3-AB and 5-aminoisoquinolinone (5-AIQ). Both of these drugs have been shown to be antagonists of PARP, and both drugs have also been demonstrated to produce neuroprotective and/or antiinflammatory actions in other disease models (Wallis et al., 1996; Hendryk et al., 2008; Zaffini et al., 2016). The present study demonstrates that the PARP inhibitors 3-AB and 5-AIQ have antidepressant-like activity. These findings uncover PARP as a unique molecular target for the development of a novel class of antidepressants.

Materials and Methods

Laboratory Animals

The use of animals for this study was approved by the University Committee on Animal Care at East Tennessee State University. All rats were ordered from Envigo, Inc. Male Sprague-Dawley rats (225–250 g upon arrival) were used as subjects in the Porsolt swim test and were socially housed in groups of 2 to 3 per cage. Rats used as "intruders" in the social defeat paradigm were individually housed and provided enrichment per the NIH Guidelines for the Care and Use of Animals. Intruder rats were male Sprague-Dawley rats (225–250 g). In addition, a total of 14 female Sprague-Dawley rats weighing 175 to 199 g upon arrival were obtained for the social defeat paradigm, and these rats were socially housed for 6 days in the animal colony prior to fallopian tube ligature, performed as previously described (Szebeni et al., 2016). Sixteen male Long-Evans hooded rats weighing 250 to 275 g upon arrival were used as "residents" in the social defeat paradigm. A climate-controlled vivarium was utilized, and animals were kept on a 12-h-on/12-off light/dark cycle.

Social Defeat Stress (SDS)

SDS was induced as described previously (Covington and Miczek, 2001; Szebeni et al., 2016). Briefly, Long-Evans hooded rats (residents) were each mated with a female (ligated) rat for a 7-day period. On the eighth day and after removal of the female, an intruder rat was placed into the cage for a 5-minute period, and dominance was established by the resident. Defeat was produced between 9:00 AM and 10:00 AM daily for 10 consecutive days. Control rats not exposed to defeat were handled each day during this same period.

Chronic Unpredictable Stress (CUS)

CUS was performed after SDS on the same day but at random times either during the day or evening as previously described (Bondi et al., 2008; Szebeni et al., 2016). Different stressors were randomly arranged and occurred at random times during the light or dark cycle of each day for 10 consecutive days. All rats were exposed twice to each of 5 different stressors, which included a 30-minute restraint, a 1-hour shaking/crowding, 10-minute cold water (18°C) swim, a 15-minute warm water swim (25°C), and a 24-hour tipped cage. For restraint, rats were placed in a restraining device made of Plexiglas restricting movement but allowing free respiration and air circulation. In the shaking-crowding procedure, 6 rats were placed in a cardboard box atop a laboratory shaker set to produce 220 back-and-forth movements (approximately 2-in sideways deflection) per minute. Both warm and cold swims were accomplished by placing the rat in a cylindrical tank (60 cm height × 30 cm diameter) filled with water at a depth of 30 cm. For the tipped cage, the animal's home cage was tipped to one side by attaching a metal spring to one side of the cage to the cage rack for a 24-hour period. Control rats were not exposed to the stressors but were handled each day at the same time.

Sucrose Preference

Sucrose preference was performed during the final 3 days of induction of social defeat stress (days 8–10) using a procedure based on that of D'Aquila et al. (1997). Animals were given 2 bottles on their cages between 7:00 PM and 9:00 PM on each day that it was performed (the first 2 h of the dark cycle) with 1 bottle containing tap water and the other containing 0.8% sucrose. Amounts of sucrose consumed were calculated as percentages of the total amount of fluid consumed during the 2-hour period on each of the 3 days of testing. The position of the sucrose bottle (left or right) was alternated equally between groups and over days. The preference of sucrose over water was used as a measure of an animal's sensitivity to reward and expressed as a percent.

Social Interaction Test

The social interaction test was performed 24 hours after the last social defeat stress on day 11 of behavioral testing. The interaction test was conducted exactly as previously described (Brown et al., 2011). Animals were placed into a locomotor arena that was divided in half by a removable metal wire divider. The intruder was first placed into the area on one side of the divider and allowed to habituate for 5 minutes. After this period, a resident rat was placed on the other side of the divider. The amount of time spent in a defined interaction zone close to the metal divider was measured using ANY-maze video tracking (Stoelting Co).

Porsolt Swim Test

Different groups of animals were tested in the Porsolt swim test. Rats were treated using the same drug treatment regimen as with the SDS/CUS paradigm, except as noted in the combined drug treatments as noted in the Results. On day 8 of drug treatment, all animals began behavioral testing in the Porsolt swim test, also known as the forced swim stress test. All animals were tested in black cylinders measuring 36 cm in diameter, and these cylinders were filled with 23°C to 25°C water following procedures as reviewed previously (Bogdanova et al., 2013), consistent with the original procedure of Porsolt and coworkers (Porsolt et al., 1978). All animals were given a pre-swim exposure test on the first day of testing, 24 hours before the swim test session the following day. On the first day of testing, animals were exposed to the water for 15 minutes, and on the second day were given a 5-minute trial. The 2 dependent measures used for forced swim stress were the latency to first immobility episode (immobility lasting >5 seconds) and the total immobility time over the 5-minute period, both recorded on the second day of testing. All movements of the animal were recorded by behavioral scanning software (ANY-maze, Stoelting Co).

Drug Administration

All drugs used in the study, 3-aminobenzamide (product no. A0788; 3-AB), 5-AIQ hydrochloride (product no. A7479), and fluoxetine (product no. F132), were obtained from Sigma-Aldrich, Inc.

Statistical Analysis

A Grubb's test was used to remove statistical outliers from each dataset prior to analyses. Statistical analyses were otherwise performed as indicated using IBM SPSS Statistics (version 23.0), and data were graphed using GraphPad Prism (version 5.0b, GraphPad Software). An independent sample *t* test was used to analyze data generated when only 2 groups were analyzed. An ANOVA was used to test multiple group comparisons. For post-hoc statistical comparisons, a Bonferroni correction was applied (as noted) to limit Type I error in multiple posthoc comparisons. For the combined drug treatment experiment, ANOVA was followed by a Dunnett's Multiple Comparison test that focused comparisons of drug treatment groups with the vehicle control group. All data are expressed as mean ± SEM.

Results

PARP Inhibitors and the Porsolt Swim Test

An initial preliminary experiment was conducted to examine the effects of 3-AB in the Porsolt swim test. Two groups of rats received either saline vehicle or 3-AB (40 mg/kg) s.c. daily for 10 days prior to swim testing. On the 10th day of treatment and 2 hours after drug or vehicle injections, rats treated with 3-AB demonstrated a significantly decreased time spent immobile compared with saline-treated controls on day 2 of the swim test ($t_{[14]}$= 2.36, P<.05) (Figure 1A). Additionally, 3-AB-treated rats demonstrated a significant increase in the latency to immobility ($t_{[13]}$ =5.56, P<.001) (Figure 1B).

Based on these data, a more extensive experiment was conducted to examine the effect of PARP inhibitors in the Porsolt swim test. Three doses of 3-AB (0.4, 4, and 40 mg/kg) were selected for study that were in the approximate range of doses shown to be effective in other disease models (Besson et al., 2003; Zaffini et al., 2016). In addition, a second PARP inhibitor, 5-AIQ, was tested at a dose of 0.3 mg/kg i.p., a dose previously shown to have protective properties in a rat model of myocardial infarction (Wayman et al., 2001). These treatments, and an additional group of rats treated with saline vehicle, were administered once daily for 10 days prior to behavioral testing. Two additional treatment groups were analyzed, including fluoxetine (10 mg/kg i.p.) and 3-AB (40 mg/kg s.c.; denoted 3-AB x 3), both groups of which received injections 23.5, 5, and 1 hour before behavioral testing identical to the protocol followed by Lucki and colleagues (1998). A 1-way ANOVA of immobility time in the swim test revealed a significant main effect of treatment group ($F_{[6,68]}$ = 5.55, P<.001). A posthoc Bonferroni comparison of the treatment groups of 5-AIQ, 3-AB 40/mg/kg (for 10 days), 3-AB x 3, and fluoxetine was equivalent with respect to immobility times, and rats in these groups spent significantly less time immobile than rats in the vehicle group and in the rats treated with the 2 lower doses of 3-AB (0.4 and 4 mg/kg) (Figure 2A). For latency to immobility, 1-way ANOVA revealed a significant main effect of group ($F_{[6,68]}$= 9.08, P<.001) (Figure 2B). Posthoc analysis revealed that latencies of the fluoxetine group and rats treated with 40 mg/kg 3-AB for 10 days were equivalent and significantly greater than all vehicle-treated control rats. The 2 lower dose 3-AB groups, the 3-AB x 3, the 5-AIQ treated group, and the vehicle control group did not significantly differ from one another. The statistical results of all group comparisons are shown in Supplemental Table 1.

A third experiment was performed to determine whether 3-AB would increase the antidepressant activity of fluoxetine, again using the Porsolt swim test. Rats were treated with a dose of 3-AB (4 mg/kg; administered 3 times over 24 hours) that was not observed in previous experiments to produce a significant effect on immobility time or latency to immobility (see Figure 2A-B). A dose of fluoxetine (2.5 mg/kg; administered 3 times over 24 hours) was chosen that was expected to produce a less than maximal antidepressant response in the swim test (Broom et al., 2002). Both drugs were also administered together at the same doses and treatment schedule, as was saline vehicle. Analysis of data from this experiment revealed a significant group main effect on both immobility time ($F = 4.32_{[3,31]}$, P = .01; Figure 3A) and latency to immobility ($F = 5.20_{[3,32]}$, P = .006; Figure 3B). A Dunnett's test was used to compare each drug treatment group to the vehicle-treated group. Both 3-AB and fluoxetine alone did not significantly affect either immobility time or latency, while the combined treatment significantly reduced immobility (P<.01) and significantly increased latency to immobility (P<.01).

Drugs that increase locomotor activity can produce false positives in the Porsolt swim test. To consider the possibility that PARP inhibitors stimulate locomotor activity, 2 measures of activity were assessed for all rats of the second and third Porsolt swim experiments. Swim speed was assessed during the Porsolt swim procedure. Locomotor activity was measured in an open field 24 hours after the second day of the Porsolt swim test, at the same time after drug or vehicle injections as was performed for the swim test. There were no significant group differences in swim speed during the Porsolt swim test ($F_{[6,67]}$= 1.57, P=.170; Figure 4A) or in locomotor activity tested the following day ($F_{[6,67]}$=0.956, P=.463; Figure 4B) in the second experiment (corresponding to Figure 2). Likewise, no significant group differences in swim speed ($F_{[3,31]}$=0.487, P=.69; Figure 4C) or locomotor activity ($F_{[3,31]}$=1.03, P=.37; Figure 4D) were observed in the third experiment (corresponding to Figure 3).

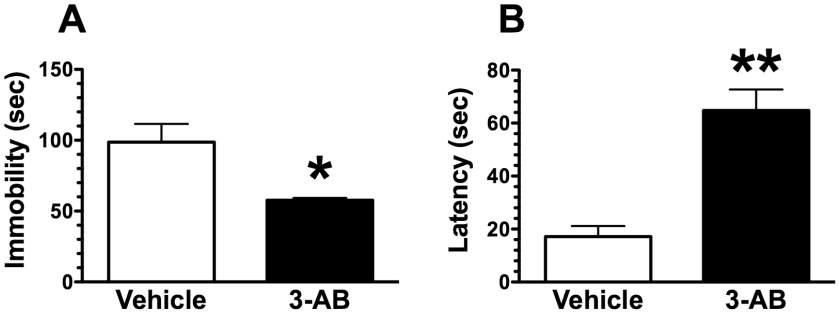

Figure 1. Preliminary experiment examining the effects of 3-aminobenzamide (3-AB) in the Porsolt swim test. 3-AB (40 mg/kg; n = 8) or vehicle (n = 10) was administered s.c. daily for 10 days prior to the swim test. Swim test data were collected on the 10th day of treatment, 2 hours after drug or vehicle injection. Total time spent immobile in the tank (A) and the latency time to immobility (B) were measured. The asterisks indicate statistical significance (*P < .05, **P < .001).

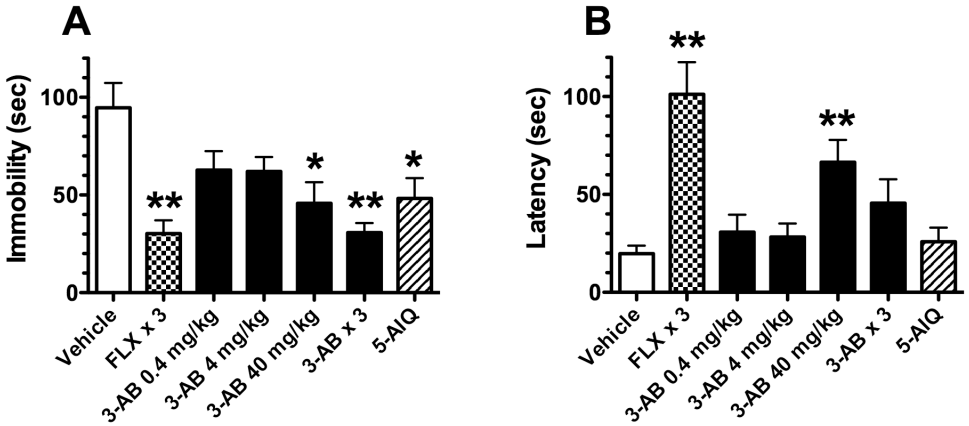

Figure 2. Effect of poly(ADP-ribose) polymerase (PARP) inhibitors on immobility time (A) and latency to immobility (B) in the Porsolt swim test. Rats were treated daily for 10 days prior to the swim test with either saline (vehicle i.p.: n=13), 3-aminobenzamide (3-AB) administered at 3 different doses as noted (s.c.; n=8-10), or 5-AIQ (0.3 mg/kg i.p.; n=9). Additional groups of rats were administered 3 injections over 24 hours prior to the swim test with either fluoxetine (10 mg/kg i.p. per injection; n=10; FLX x 3) or 3-AB (40 mg/kg s.c. per injection; n=7; 3-AB x 3). The swim test data were collected 2 h after the final drug or vehicle injection. Asterisks indicate significant differences compared to the vehicle group (*$P<.05$, **$P<.01$). The results of statistical analyses of all other comparisons can be found in Supplemental Table 1.

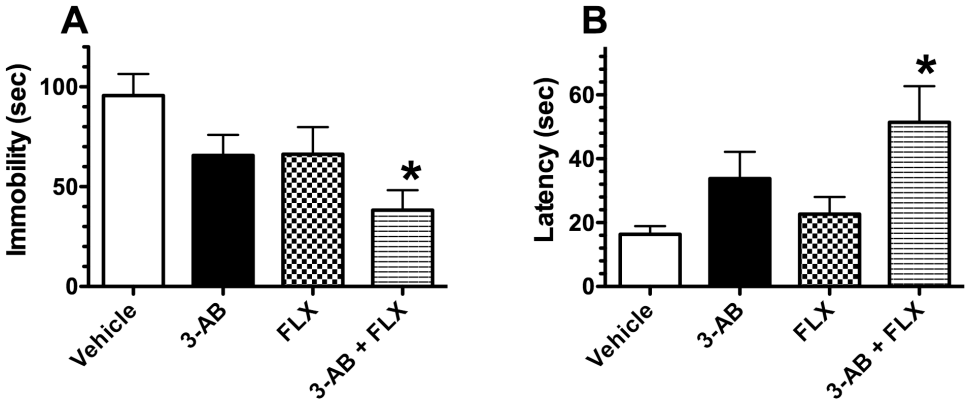

Figure 3. Effect of combined treatment of 3-aminobenzamide (3-AB) and fluoxetine (FLX) on immobility time (A) and latency to immobility (B) in the Porsolt swim test. Rats were administered 3 injections over 24 hours prior to the swim test with either vehicle (i.p.; n=11), 3-AB (4 mg/kg s.c.; n=7), FLX (2.5 mg/kg i.p.; n=7), or 3-AB (4 mg/kg s.c.) plus FLX (2.5 mg/kg i.p.; n=6–7). The swim test data were collected 2 h after the final drug or vehicle injection. Asterisks indicate significant differences comparing each drug-treated group with the vehicle group (*$P<.01$).

PARP Inhibitors and Combined and Repeated Social Defeat and Unpredictable Stress

Experiments were performed to determine whether the PARP inhibitor 3-AB would block the behavioral effects of repeated psychological stress. Rats were treated with vehicle, fluoxetine (10 mg/kg i.p. daily), or 3-AB (40 mg/kg s.c. daily) 2 hours prior to the social defeat procedure each day for 10 days. These rats were also exposed daily to an unpredictable stressor. Rats receiving vehicle but no exposure to the 2 daily stressors served as a control group. ANOVA revealed a significant main effect of group ($F_{[3,28]}=12.91$, $P=2.7\times10^{-5}$) (Figure 5A) on sucrose preference. Posthoc analysis showed that vehicle-treated stressed rats had a robust reduction in sucrose preference relative to nonstressed control rats ($P=1.1\times10^{-5}$). Sucrose preference was significantly higher in stressed rats treated with 3-AB ($P=.024$) or fluoxetine ($P=.005$) compared with stressed rats treated with vehicle, while 3-AB and fluoxetine groups did not significantly differ. There was also a significant group main effect on time spent in the interaction zone ($F_{[3,29]}=3.23$, $P=.03$) (Figure 5B). Vehicle-treated rats exposed to the stressors had a robust reduction of time in the interaction zone compared with control rats ($P=.008$). Rats treated with 3-AB and exposed to stressors exhibited significantly greater interaction times compared with vehicle-treated rats exposed to stressors ($P=.014$). Interaction times of the fluoxetine-treated rats appeared to be greater than that of vehicle-treated rats exposed to stress, although this difference did not reach statistical significance ($P=.073$). The statistical results of all group comparisons of sucrose preference and interaction times are shown in Supplemental Table 2.

Discussion

The present study is the first to demonstrate the ability of PARP inhibitors to counteract the deleterious effects of psychological stress on rodent behaviors and to produce antidepressant-like activity. Two structurally different PARP inhibitors, 3-AB and 5-AIQ, demonstrated antidepressant-like activity in the Porsolt swim test. Both 3-AB and 5-AIQ produced their antidepressant-like responses in the swim test at doses that did not significantly affect locomotor activity or swim speed, suggesting that reduced immobility produced by these drugs was not secondary to a stimulant effect of the compounds. In addition, the combination of 3-AB plus fluoxetine produces antidepressant-like effects in the swim test at doses that did not produce a significant effect for either drug when administered alone,

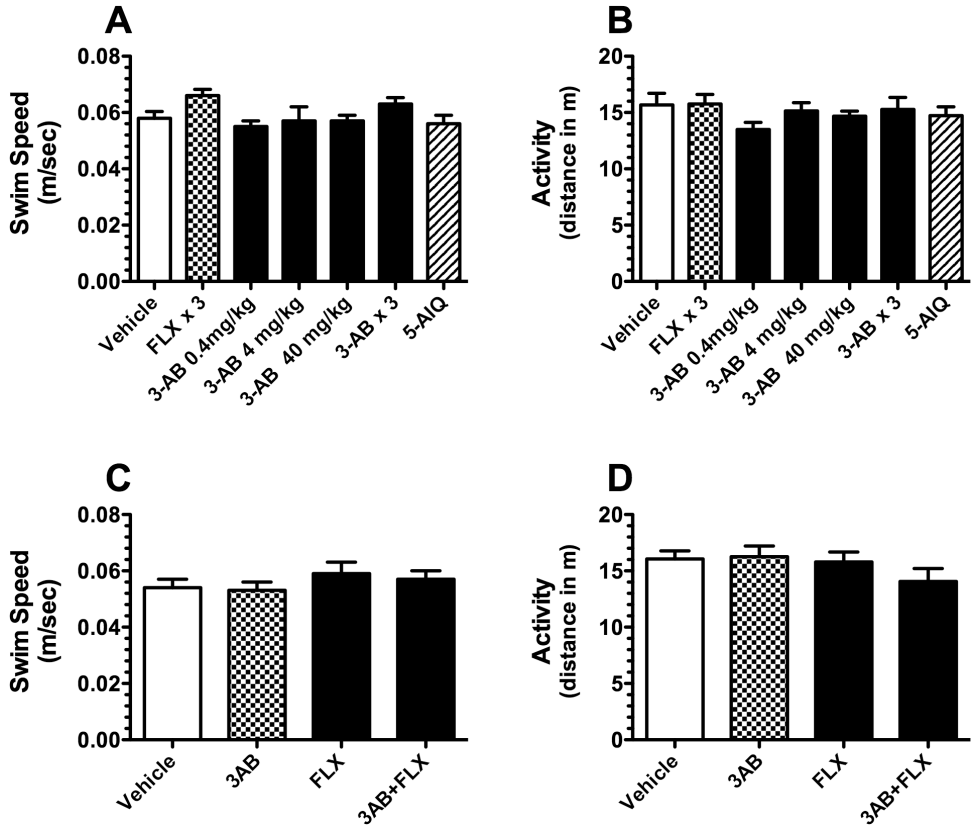

Figure 4. Swim speeds (A and C) and locomotor activities (B and D) of swim test rats. A and B are data from rats of treatment groups studied in Figure 2; C and D are data from rats of treatment groups studied in Figure 3. Swim speed was measured during the swim test, and locomotor activity was measured 24 hours after the second day of the Porsolt swim test, both of which were measured 2 hours after drug or vehicle injection. There were no significant group effects observed for swim speed or locomotor activity in either experiment. Sample sizes are as noted in Figures 2 and 3.

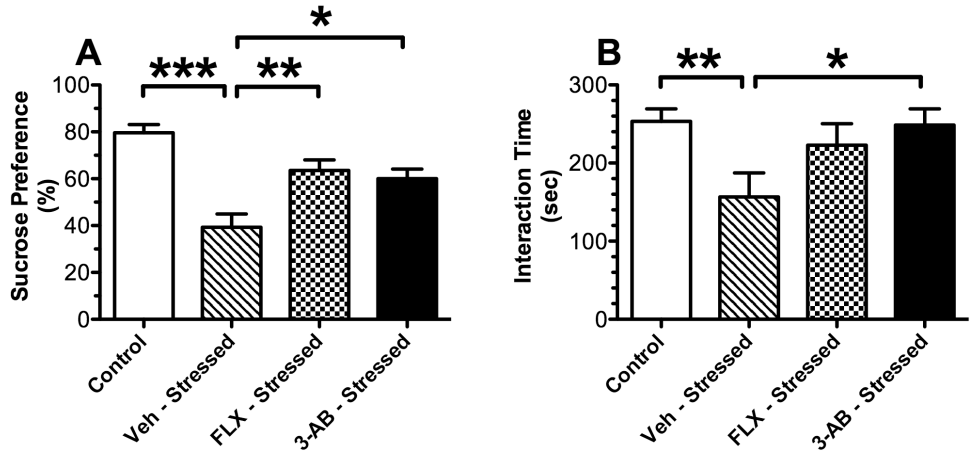

Figure 5. Effect of 3-aminobenzamide (3-AB) on sucrose preference (A) and interaction time (B) in rats exposed to repeated psychological stressors. Treatment groups included handled control rats not exposed to stressors (Control; n=7) and rats exposed to stressors and administered once daily injections of saline vehicle (i.p.; Veh-Stressed; n=7), fluoxetine (10 mg/kg i.p.; n=8), or 3-AB (40 mg/kg s.c.; n=7). Stressed rats were exposed to social defeat and unpredictable stress each day for 10 days. Statistical results of specific group comparisons are indicated by horizontal lines above bars, with asterisks indicating significance (*$P<.05$, **$P<.01$, ***$P<.0001$). Statistical results of all comparisons are provided in Supplemental Table 2.

suggesting that combination therapy is a reasonable possibility. Finally, 3-AB protected rats from the development of anhedonia and deficits in social interaction following repeated exposure to psychological stressors. These intriguing findings open the door to the potential development of a truly novel class of antidepressant drugs.

PARP1 is a key nuclear enzyme of the DNA base excision repair apparatus that is activated by double- or single-strand breaks, such as can occur secondary to oxidative attack of nucleotides by free radicals. PARP1 is a member of a subfamily of 3 PARPs (PARP1, PARP2, and PARP3) that covalently build PAR polymers onto many different proteins as a mechanism to

regulate a variety of cellular functions. PARP1 is expressed in many mammalian brain regions, and its gene expression in the brain appears to be highest among the PARP1, PARP2, and PARP3 enzymes (2010 Allen Institute for Brain Science, Allen Mouse Brain Atlas, available from http://mouse.brain-map.org). PAR polymers are bulky and charged, and addition of PAR polymers to nuclear proteins by PARP1 can modify protein-protein and protein-DNA interactions. Target proteins of PARP1-mediated PARylation include itself, histones, and transcription factors resulting in chromatin remodeling and regulation of gene transcription. DNA damage repair is facilitated by PARP1, but PARP1 also facilitates NF-κB-mediated inflammatory responses (Martínez-Zamudio and Ha, 2014), and PARP1 can directly bind to promoter regions as a transcription factor (Ambrose et al., 2007). Under conditions of excessive PARP1 activation, cell death can ensue due to depletion of cellular NAD^+, the substrate of PARylation (Berger, 1985). Recent studies demonstrate that PARP1 also has PARylation-independent effects on gene expression of inflammatory mediators (Ha et al., 2002), and it can be activated by TNFα independently from DNA damage (Vuong et al., 2015).

Drugs that inhibit PARP have therapeutic potential in a number of different conditions. The anti-cancer properties of PARP inhibitors are well known. Since cancer cells exploit PARP1 to protect themselves from death secondary to DNA lesions, PARP1 inhibitors facilitate the anti-cancer effects of DNA damaging anti-cancer drugs (e.g., cisplatin) and radiation therapy. Numerous PARP1 inhibitors are in clinical trials for cancer and one is currently marketed (olaparib, Astra-Zeneca, Inc.). With regards to the ability of PARP1 to facilitate NF-κB activation, PARP inhibitors have been recently demonstrated to have anti-inflammatory and neuroprotective actions in a number of different conditions associated with inflammation, including chronic asthma (Zaffini et al., 2016), myocardial infarction (Wayman et al., 2001), stress-evoked immunocompromise (Drazen et al., 2001), traumatic brain injury (Besson et al., 2003), and cerebral ischemia (Gerace et al., 2012). In the context of the antiinflammatory effects of PARP inhibitors, there has been a recent reemergence of interest in the role of inflammation in depressive disorders, although this continues to be a matter of debate (Mechawar and Savitz, 2016). Elevated expression of inflammatory cytokines, IL1β and TNFα, has been observed in human MDD patients and/or suicide victims (Shelton et al., 2011; Pandey et al., 2012; Rizavi et al., 2016). Interestingly, inhibition of PARP1 blocks immune stimulation-induced increases in TNFα and IL1β (Hassa and Hottiger, 2002). Although the poor affinity of 3-AB for PARP-1 has precluded its use as a cancer therapy (Calvert and Azzariti, 2011), its putative efficacy for treating depressive symptoms demonstrated here suggests action through a different mechanism in which lower affinity is functional and possibly preferable. Hence, it seems possible that the ability of PARP1 inhibitors to produce antidepressant-like effects in rodents is related to the antiinflammatory effects of these drugs, although other possible mechanisms may be at work as well.

PARP1 is activated under conditions of elevated oxidative stress (Liu et al., 2000; Lan et al., 2003; Adaikalakoteswari et al., 2007), and numerous studies suggest that MDD is associated with elevated oxidative stress (Maes et al., 2011; Maurya et al., 2016). Likewise, rodents exposed to psychological stress demonstrate oxidative stress conditions in the brain (Che et al., 2015; Mejia-Carmona et al., 2015; Réus et al., 2015). Because oligodendrocytes are highly sensitive to oxidative stress (Kim and Kim, 1991; Connor and Menzies, 1996; Thorburne and Juurlink, 1996; Juurlink et al., 1998), they can be viewed as a "canary in the coal mine" for detecting oxidative stress conditions in the brain. Recently, Szebeni et al. (2014, 2016) studied indices of oxidative stress in oligodendrocytes laser captured from psychiatrically normal and MDD brain donors. This research demonstrated elevated levels of DNA oxidation, shortened telomeres, reduced gene expression of antioxidant enzymes, and elevated gene expression of PARP1 in prefrontal cortical white matter from MDD brain donors compared with matched normal control donors. Although PARP1 protein and activity were not measured in that study, others have shown that PARP1 gene expression is upregulated under oxidative stress conditions in tandem with PARP activity levels (Adaikalakoteswari et al., 2007). Hence, these data draw attention to the possibility that PARP1 upregulation in MDD may contribute to cellular demise that contributes mechanistically to behavioral sequelae related to the disorder. The ability of PARP inhibitors to produce antidepressant-like actions in rodent behavioral models in the present study further supports the role of PARP1 in depression pathophysiology.

The rodent model of repeated stress in this study is rather unique in that 2 stressors were administered as we have previously reported (Szebeni et al., 2016). The rationale for using this double stress model was to reduce the likelihood of stress resilience. Nestler and colleagues have constructed a theory of a "neurobiology of resilience" that occurs in both rodents and humans, wherein the rodent may be more well adapted to develop resilience to stressors evolutionarily (Krishnan et al., 2007; Russo et al., 2012). Since SDS is typically performed at the same time each day, the rodent can predict over time when the stressor will occur, possibly enhancing resilience. Humans rarely experience stressors at the same time each day, a fact that weakens the construct validity of SDS. We suggest that the combination of a mild (Riaz et al., 2015) stressor of unpredictable nature (CUS) to the paradigm of SDS improves construct validity and presumably minimizes the likelihood of rats to demonstrate resilience.

PARP inhibitors have been shown to interfere with the formation of long-term potentiation (LTP) and can disrupt long-term memory formation in *Aplysia* bathed in inhibitors (Cohen-Armon et al., 2004) and in mice when inhibitors are infused into the cerebral ventricles (Goldberg et al., 2009). PARP knockout mice also demonstrate defects in LTP formation (Visochek et al., 2016). It is difficult to compare the levels of PARP inhibition in these studies with those achieved by doses of PARP inhibitors administered subcutaneously or intraperitoneally to rats in the present study. It is noted that PARP inhibitors (olaparib and niraparib) are currently FDA approved for the treatment of specific cancers, and at the current time reports of disruption of memory in humans taking these medications is absent in the published literature. Rather, there is growing interest in PARP1 as a therapeutic target for the treatment of Alzheimer's disease (Abeti et al., 2011; Martire et al., 2015; Wang et al., 2015). The combined SDS/CUS model used in the present study is likely to have a memory component associated with it such that pretreatment with PARP inhibitors could interfere with the formation of the memory of stressful events in the model. Moreover, forced swim-induced behavioral despair (increased immobility time) requires the formation of LTP in the hippocampus (Jing et al., 2015), effects that are blocked by NMDA receptor antagonists (ketamine, MK-801) with known antidepressant activity (Berman et al., 2000; Trullas and Skolnick, 1990). In fact, suppression of hippocampal LTP has been observed following treatment of rats with several antidepressant drugs, including trimipramine (Massicotte et al. 1993), fluoxetine (Shakesby et al., 2002; Stewart and Reid, 2000;

Rubio et al., 2013), fluvoxamine (Kojima et al., 2003), escitalopram (Mnie-Filali et al., 2006), and milnacipram (Tachibana et al., 2004). Hence, the potential role of LTP inhibition in mediating possible memory-disrupting effects or antidepressant-like activity of PARP inhibitors in rats warrants further study. In addition, direct effects of 3-AB or 5-AIQ on monoamine receptors or transporters have not been described. Although neither 3-AB nor 5-AIQ are catecholamine like or tryptamine like, an exploration of potential secondary effects of these drugs on biological amines will be important to clarify the mechanism of their antidepressant-like activity.

Inadequate or incomplete treatment of MDD using currently available antidepressant drugs is a major health and economic issue (Thase, 2009). Unfortunately, antidepressants that are newer to the market have not substantially mitigated this problem, because these new drugs do not demonstrate a significantly greater therapeutic efficacy than older drugs, with minor exceptions (Montgomery et al., 2007; Papakostas et al., 2007). Given therapeutic shortcomings of current antidepressants, it is imperative that novel drug targets be identified to improve the efficacy of existing antidepressants through adjuvant treatments or provide therapeutic alternatives to the many who do not respond. The use of ketamine represents the first noteworthy recent advance in the field, although some major concerns remain about its efficacy (Murrough, 2016), side effects, and its potential for diversion (Sassano-Higgins et al., 2016). The primary actions of current commonly prescribed antidepressants involve modulation of the transmission of noradrenergic and serotonergic neurons. The present study demonstrates antidepressant-like behavioral effects of PARP inhibitors in 2 different animal models used typically to screen drugs for antidepressant activity in humans. Given that PARP inhibitors have no known direct effects on brain norepinephrine or serotonin, the findings here strongly implicate PARP inhibitors as an entirely novel type of antidepressant. Results here also suggest that PARP inhibitors could be used as an adjuvant to existing antidepressant treatments. The potential use of PARP inhibitors as antidepressants in humans will require that adequate safety testing is completed, particularly focusing on potential toxicities of these compounds that could result from interfering with the multiple cellular systems that are impacted by these drugs (Passeri et al., 2016). The mechanisms involved in antidepressant-like effects of the PARP inhibitors that were tested are presumed to be mediated primarily through inhibition of PARP. The role of secondary effects of PARP inhibitors in antidepressant actions, for example, suppression of LTP, antiinflammatory effects, protection from oxidative stress-induced NAD^+ depletion, and potential effects on monoamine or glutamate transmitters, remain to be determined.

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Statement of Interest

Gregory A. Ordway, Attila Szebeni, and Russell W. Brown are co-inventors of a patent application regarding PARP inhibitors as drugs to treat psychological stress-related disorders such as major depressive disorder.

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