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Chronic administration of quetiapine stimulates dorsal hippocampal proliferation and immature neurons of male rats, but does not reverse psychosocial stress-induced hyponeophagic behavior

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ABSTRACT

Quetiapine, an atypical antipsychotic, has been used for the treatment of several neuropsychiatric disorders. However, the underlying mechanism of the broad therapeutic range of quetiapine remains unknown. We previously reported that several aversive conditions affect dorsal/ventral hippocampal neurogenesis differentially. This study was aimed to elucidate the positive effects of chronic treatment with quetiapine on regional differences in hippocampal proliferation and immature neurons and behavioral changes under psychosocial stress using the Resident-Intruder paradigm. Twenty-three male Sprague-Dawley rats were intraperitoneally administered a vehicle or quetiapine (10 mg/kg) once daily for 28 days. Two weeks after starting the injections, animals were exposed to intermittent social defeat (four times over two weeks). The behavioral effects of stress and quetiapine were evaluated by the Novelty-Suppressed Feeding (NSF) test. The stereological quantification of hippocampal neurogenesis was estimated using immunostaining with Ki-67 and doublecortin (DCX). Chronic quetiapine treatment stimulated the Ki-67- and DCX-positive cells in the dorsal hippocampus, but not in the ventral subregion. The stress-induced changes in neurogenesis and hyponeophagic behavior were not reversed by repeated administration of quetiapine. Future study with additional behavioral tests is needed to elucidate the functional significance of the quetiapine-induced increase in dorsal hippocampal neurogenesis.

1. Introduction

Antipsychotics that are effective therapeutics for schizophrenia are categorized into typical and atypical antipsychotics based on the differences in action mechanisms. In the past decades, atypical antipsychotics are considered the first choice for the treatment of schizophrenia because of their good efficacy, safety, and tolerability (Kane and Correll, 2010). Quetiapine (QTP) is a unique atypical antipsychotic with a greater affinity for serotonin 5-HT_2 receptors than for dopamine D_2 receptors and a partial agonist activity at 5-HT_{1A} receptors, together with considerable activities at histamine H_1 receptors and α_1- and α_2-adrenergic receptors (Nemeroff et al., 2002). Of interest, several clinical studies and reviews have demonstrated that monotherapy with QTP is effective for the treatment of major depressive disorder (Cutler et al., 2009; Ignácio et al., 2018; Maneeton et al., 2012; McIntyre et al., 2009; Weisler et al., 2009, 2012) and bipolar disorder (Altamura et al., 2003; Calabrese et al., 2005; Muneer, 2015; Sanford and Keating, 2012; Suttajit et al., 2014). However, the underlying mechanisms of the broad therapeutic range of QTP for the neuropsychiatric symptoms remain unknown.

Neurogenesis is a process of generating functionally integrated neurons from progenitor cells. In the adult mammalian brain, neural stem cells are located mainly in the two canonical neurogenic sites, the subventricular zone (SVZ) of the lateral ventricle and the subgranular zone (SGZ) of the hippocampal dentate gyrus (DG). Adult neurogenesis also occurs in other neurogenic niches, such as the hypothalamus, amygdala, substantia nigra, striatum, and neocortex (Lee and Blackshaw, 2012; Rojczyk-Gołębiewska et al., 2014; Rusznák et al., 2016). The hippocampus is anatomically and functionally differentiated along a dorso-ventral (septo-temporal) axis: the dorsal (septal) region is involved in cognitive function, while the ventral (temporal) region is linked to regulations of emotion and stress response (Moser and Moser,

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1998; Sahay and Hen, 2007; Tanti and Belzung, 2013). Thus, adult neurogenesis in the hippocampus has been reported to be involved in several neuropsychiatric disorders, including depression (Duman, 2004; Samuels and Hen, 2011; Santarelli et al., 2003; Schoenfeld and Gould, 2012), schizophrenia (Flagstad et al., 2005; Keilhoff et al., 2004; Pieper et al., 2005), and cognitive deficits with neurodegenerative diseases (Marlatt and Lucassen, 2010; Mu and Gage, 2011; Vivar, 2015). Several rodent studies have indicated that chronic treatment with atypical antipsychotic agents, but not typical antipsychotics, leads to the stimulation of cell proliferation, survival, and neurogenesis in the hippocampal SGZ (Chen et al., 2013; Chikama et al., 2017; Halim et al., 2004; Kodama et al., 2004; Luo et al., 2005; Morais et al., 2017; Wakade et al., 2002; Xu et al., 2006; Xue et al., 2017). However, little has been studied on the presence/absence of these regional differences in the positive effects of atypical antipsychotics on adult hippocampal neurogenesis.

We previously reported that hippocampal neurogenesis in the dorsal and ventral DG is differentially affected by several aversive conditions such as the Resident-Intruder paradigm (psychosocial stressor), a Communication Box (emotional stressor), or prolonged sleep deprivation (Murata et al., 2015, 2017, 2018). Also, in our previous study, chronic administration of tandospirone, a clinically available 5-HT_{1A} receptor partial agonistic anxiolytic, reversed the social defeat-induced decrease in hippocampal neurogenesis, which is associated with the blocking effect on the stress-induced abnormal behavioral changes assessed by the Novelty-Suppressed Feeding (NSF) test (Murata et al., 2015).

The present study was conducted to elucidate regional differences in the positive effects of chronic treatment with QTP on hippocampal neurogenesis under psychosocial stress using the Resident-Intruder paradigm. We also performed the NSF test, which has been validated for the evaluation of the chronic effect of agents with antidepressive potential (Bodnoff et al., 1989; Dulawa and Hen, 2005).

2. Methods

2.1. Animals and housing conditions

Naïve male Sprague-Dawley rats (Kyudo Co., LTD., Tosu, Japan) weighing 150–200 g at seven weeks of age upon arrival served as stress-exposed animals. Each subject was housed individually in a temperature (23 ± 2 °C), humidity (60 ± 10%), and light-controlled room (reversed 12-h light/dark cycle, lights off at 7:00 a.m.). Food and water were available ad libitum.

For generating the psychosocial stress paradigm, resident colonies were established that consisted of two male Sprague–Dawley rats (1 year of age, weight 600–800 g, called as resident rats), and one female rat (6 weeks of age) to increase aggression and territorial behavior, as previously described (Murata et al., 2015). Resident rats were housed in larger polycarbonate cages (50 × 40 × 20 cm) compared to standard group-housing cages and were on a reversed 12 h light/dark cycle.

All animal care and use procedures were performed in compliance with the regulations established by the Experimental Animal Care and Use Committee of Fukuoka University, which are in accordance with the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publications No. 8023, revised 1978).

2.2. Drug administration

Quetiapine hemifumarate was purchased from Toronto Research Chemicals Inc. (Ontario, Canada). The drug was dissolved in saline with 0.8% acetic acid and prepared at a concentration of 10 mg/mL as needed. The animals were intraperitoneally injected with QTP or vehicle (saline with 0.8% acetic acid) in a volume of 1 mL/kg. The dosage of QTP was determined according to previous reports (Luo et al., 2005; Xu et al., 2002).

2.3. Social defeat procedure by resident-intruder paradigm

The social defeat procedure in this study was the same as that adopted in our previous study (Murata et al., 2015). Briefly, resident colonies were trained with the introduction of a naïve non-subject training intruder rat three times over a period of 1 month before subject testing. Colonies were selected for inclusion in the study based on resident rats fulfilling the aggression criteria of consistent biting and pinning down of non-subject training intruder rats within the first 10 min of their introduction.

For testing, ten minutes after the female was removed, a 9 weeks of age naïve young male Sprague-Dawley rat (as the intruder), was placed in the colony for 20 min. Intruder rats were typically pinned down by the larger, more aggressive resident rats and exhibited submissive posture within 10 min after introduction into the colony cage. After the 20 min session, intruders were returned to their home cages. None of the intruders were exposed to the same residents on consecutive days or more than twice during the procedure. All intruders were psychosocially defeated by the resident rat in all stress sessions in the present study.

To control for the effects of the novel environment only, naïve rats were subjected to novel cage stress, designated as control rats. They were removed from their home cages and placed alone in a new room and a new, non-colony, larger size cage with fresh bedding for 20 min.

2.4. Experimental design

The animals were acclimated for one week after arrival, then subjected to four weeks administration of drugs and four times to intermittent stress exposure. Twenty-three male Sprague–Dawley rats were randomly assigned to the following four experimental groups (n = 5–6 per group). (1) *Control* group (n = 5) animals were treated with an intraperitoneal injection of saline with 0.8% acetic acid (1 mL/kg) daily for 28 days and four times intermittently subjected to a novel cage, once every 72–96 h over the course of 11 days, beginning two weeks after the start of treatment. (2) *Stress* group (n = 6) animals were treated with an intraperitoneal injection of saline with 0.8% acetic acid (1 mL/kg) daily for 28 days and four times subjected to intermittent social defeat, once every 72–96 h over the course of 11 days, beginning two weeks after the start of treatment. (3) *Quetiapine* + *Control* group (n = 6) animals were treated with an intraperitoneal injection of QTP (10 mg/kg) daily for 28 days and four times intermittently subjected to a novel cage, once every 72–96 h over the course of 11 days, beginning two weeks after the start of treatment. (4) *Quetiapine* + *Stress* group (n = 6) animals were treated with an intraperitoneal injection of QTP (10 mg/kg) daily for 28 days and four times subjected to intermittent social defeat, once every 72–96 h over the course of 11 days, beginning two weeks after the start of treatment. The experimental design is shown in Fig. 1.

2.5. Novelty-Suppressed Feeding (NSF) test

NSF testing was performed as previously described (Mori et al., 2014; Murata et al., 2015). For testing, rats were food-deprived for 24 h, then placed in a corner of a rectangle open field (50 × 40 × 20 cm) with a food pellet put in the center. The time to the first chewing of the food (latency) was recorded. The test was continued for up to 12 min and if the animal had not eaten the latency was scored as 12 min. The drug treatment was done for 28 days, and the next day the rats were subjected to the NSF test.

2.6. Brain slice preparation

Two hours after termination of the NSF test, the rats were deeply anesthetized with sodium pentobarbital and perfused transcardially with saline (1000 mL/kg) followed by 400 mL of 4% ice-cold

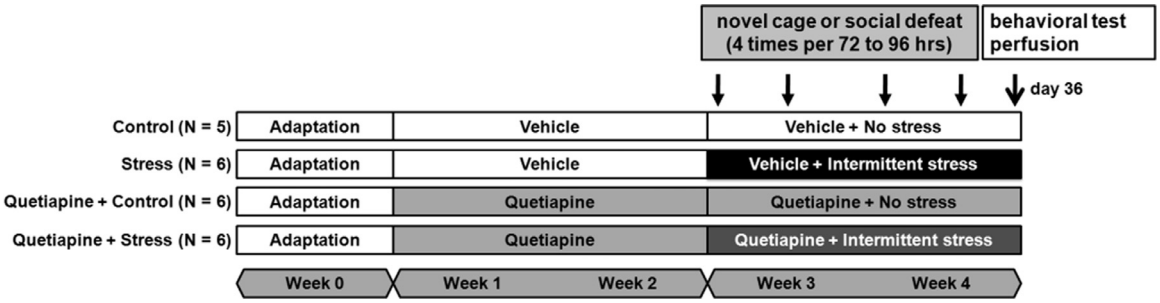

Fig. 1. Experimental design. (1) *Control* group (n = 5) animals were treated with an intraperitoneal injection of vehicle (1 mL/kg) daily for 28 days and four times intermittently subjected to a novel cage, once every 72–96 h over the course of 11 days, beginning two weeks after the start of treatment. (2) *Stress* group (n = 6) animals were treated with an intraperitoneal injection of vehicle (1 mL/kg) daily for 28 days and four times subjected to intermittent social defeat, once every 72–96 h over the course of 11 days, beginning two weeks after the start of treatment. (3) *Quetiapine* + *Control* group (n = 6) animals were treated with an intraperitoneal injection of quetiapine (10 mg/kg) daily for 28 days and four times intermittently subjected to a novel cage, once every 72–96 h over the course of 11 days, beginning two weeks after the start of treatment. (4) *Quetiapine* + *Stress* group (n = 6) animals were treated with an intraperitoneal injection of quetiapine (10 mg/kg) daily for 28 days and four times subjected to intermittent social defeat, once every 72–96 h over the course of 11 days, beginning two weeks after the start of treatment. In all groups, on the day after the last injection, animals were subjected to a behavioral test, then perfused transcardially with a fixative for the evaluation of hippocampal neurogenesis.

paraformaldehyde in 0.1 M phosphate buffered saline (PBS; pH 7.4). The whole brain was removed from the skull and incubated in the same fixative at 4 °C for 24 h. Post-fixed brain was soaked into 15% sucrose in PBS at 4 °C, then placed into 30% sucrose in PBS at 4 °C for cryoprotection. Serial sections of the brain were cut coronally at 40 µm-thick through the entire hippocampus (bregma –1.72 to –6.84 mm; Paxinos and Watson, 2007) on a freezing microtome. Sections were mounted onto silane-coated glass slides, then dried and stored at –80 °C prior to processing.

2.7. Immunohistochemistry

For immunostaining of Ki-67 and doublecortin (DCX), Serial sections through the entire hippocampus were collected every 8 sections. Similar to our previous work (Murata et al., 2015), rabbit anti-Ki-67 (1 : 500, ab15580, RRID: AB_443209, Abcam, Cambridge, UK) and goat anti-DCX (1 : 250, sc-8066, RRID: AB_2088494, Santa Cruz, CA, USA) were used as primary antibodies. After washing in PBS, sections were incubated for 30 min in 3% H_2O_2 to eliminate endogenous peroxidases. After blocking with 5% normal serum (normal goat serum for Ki-67; normal horse serum for DCX, Vector Laboratories, Burlingame, CA, USA), the sections were incubated with each primary antibody overnight at 4 °C. They were then rinsed in PBS and incubated for 2-h with secondary antibody (biotinylated goat anti-rabbit IgG [BA-1000, RRID: AB_2313606] for Ki-67; biotinylated horse anti-goat IgG [BA-9500, RRID: AB_2336123] for DCX; both diluted 1:200, Vector Laboratories, Burlingame, CA, USA) followed by amplification with streptavidin-biotin complex (1:300, DAKO Japan, Kyoto, Japan), then the cells were visualized with diaminobenzidine (Vector Laboratories, Burlingame, CA, USA). The sections were air-dried and counterstained with 5% hematoxylin, then dehydrated in graded alcohol, cleared in xylene, and coverslipped.

2.8. Stereological analysis of Ki-67- and doublecortin (DCX)-positive cells in the dentate gyrus

The quantification of Ki-67- and DCX-positive cells was according to previous description (Mori et al., 2014; Murata et al., 2015). Ki-67-immunoreactive cells were counted in the SGZ of the DG using a 40 × objective (DMD108, Leica Microsystems, Wetzlar, Germany). Cells in the uppermost focal plane of the section were excluded. Total cell number was calculated by multiplying the number of cells counted by the inverse of the section sampling fraction, i.e. eight.

The total number of DCX-positive cells was counted throughout the rostrocaudal extent of the DG of the granule cell layer (GCL) using a 40 × objective lens (Nikon E600, Nikon, Tokyo, Japan). Briefly, the contour of the GCL/SGZ was first delineated in every section for counting using the tracing function of the StereoInvestigator (MicroBrightField Japan, Tokyo, Japan) software. Following this, the optical fractionator component was activated by entering the following parameters: grid size (250 × 150 μm^2), counting frame size (75 × 75 μm^2), thickness of the guard zone (5 µm), and optical dissector height (20 µm). A computer-driven motorized stage then randomly determined the counting frame locations. The StereoInvestigator software used the optical fractionator formula to calculate the total number of DCX-positive cells per DG. Every eighth section throughout the DG was analyzed, yielding a mean of 16 sections per brain. We estimated the total number of DCX-labeled cells in the GCL together with the SGZ, which is defined as a two-cell-body-wide zone along the border of the GCL. This procedure ensured a systematic random sample of the sections in which all parts of the DG region analyzed had the same opportunity of being represented. The precision of estimates of the number of cells was expressed using the coefficient of error (CE). The stereological sampling scheme was considered adequate when CE was less than 0.10 (West and Gundersen, 1990). The volume of the GCL, including the SGZ, was calculated separately using Cavalieri's principle (Gundersen et al., 1988). The density score (cells/mm^3) for DCX-positive cells was generated by dividing the stereological estimate of the DCX-positive cell number in the GCL by the total volume of the GCL.

In addition, the total numbers of Ki-67- and DCX-positive cells in the DG were also estimated separately in the dorsal-rostral (interaural 3.60–7.28 mm) and the ventral-caudal (interaural 3.60–2.28 mm) areas of the hippocampus, as described previously (Murata et al., 2015). All cell counts were performed by the same, blinded investigator (YM).

2.9. Statistical analysis

Data were statistically analyzed using StatView software Ver.5 (HULINKS, Tokyo, Japan). For quantification of Ki-67- and DCX-positive cells, group comparisons were performed using parametric tests as two-way factorial analysis of variance (ANOVA) followed by Bonferroni/Dunn *post hoc* analysis, when required. Because the latency in the NSF test did not follow a normal distribution and variance was not homogeneous, the Kruskal-Wallis test was performed followed by a Mann–Whitney *U test* that includes corrections for multiple comparisons. For the NSF test, the Kaplan–Meier method with Mantel–Cox log-rank test was used to determine differences in survival curves where the latency to eating was the limit of survival. All data are represented as mean ± standard deviation. A p value < 0.05 was adopted for significance.

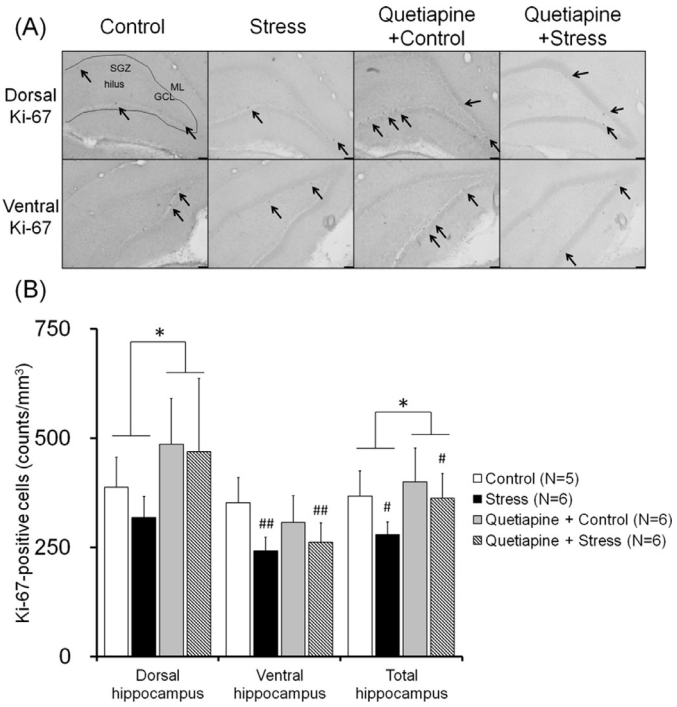

Fig. 2. Photomicrographs of representative Ki-67-immunopositive cells (A, arrowed, ×40 magnification, scale bars 100 μm) in the dentate gyrus of the dorsal (*upper panel*) and ventral (*lower panel*) hippocampus of rats. Effects of intermittent social defeat and chronic quetiapine treatment on Ki-67-positive cells (B). The density of Ki-67-labeled cells in the subgranular zone is expressed per volume of granular cell layer (GCL) in the dorsal (*left hand side*), ventral (*middle*) and total (*right hand side*) hippocampus of rats. In the total and dorsal subregion of the hippocampal dentate gyrus, chronic quetiapine treatment increased the density of Ki-67-positive cells independent of stress exposure. In contrast, psychosocial stress significantly decreased the density of Ki-67-positive cells in the total and ventral hippocampus. * $p < 0.05$ (two-way ANOVA), # $p < 0.05$, ## $p < 0.01$ (vs. control group treated with matching drugs). GCL, granular cell layer; ML, molecular layer; SGZ, subgranular zone.

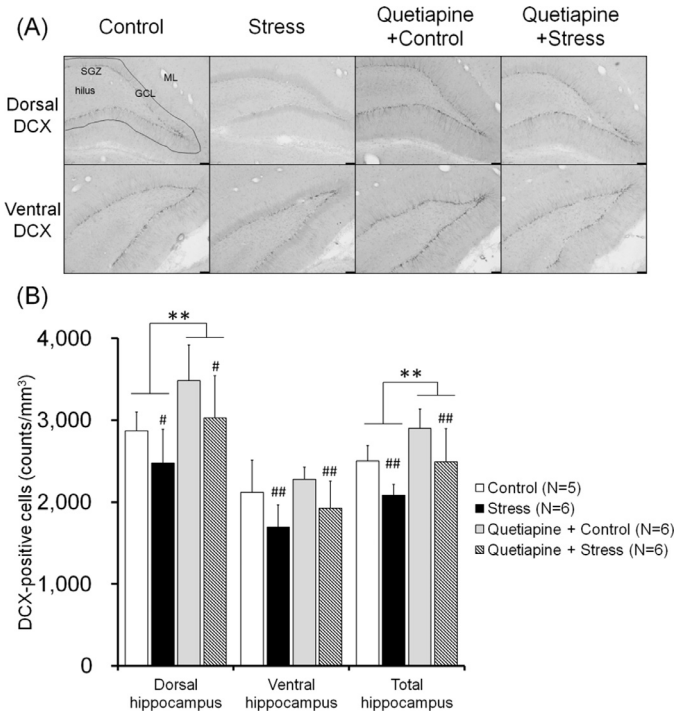

Fig. 3. Photomicrographs of representative doublecortin (DCX)-immunopositive cells (A, arrowed, ×40 magnification, scale bars 100 μm) in the dentate gyrus of the dorsal (*upper panel*) and ventral (*lower panel*) hippocampus of rats. Effects of intermittent social defeat and chronic quetiapine treatment on DCX-positive cells (B). The density of DCX-labeled cells in the subgranular zone is expressed per volume of granular cell layer (GCL) in the dorsal (*left hand side*), ventral (*middle*) and total (*right hand side*) hippocampus of rats. In the total and dorsal subregion of hippocampal dentate gyrus, chronic quetiapine treatment increased the density of DCX-positive cells independent of stress exposure. In contrast, psychosocial stress significantly decreased the density of DCX-positive cells in all subregions of the hippocampus. ** $p < 0.01$ (two-way ANOVA), # $p < 0.05$, ## $p < 0.01$ (v.s. control group treated with matching drugs). GCL, granular cell layer; ML, molecular layer; SGZ, subgranular zone.

3. Results

3.1. Ki-67- and doublecortin-positive cells in the dentate gyrus of the dorsal and ventral hippocampus

In all experiments, no severe wounds were discovered on intruder's bodies as a result of the stressful encounters. Most of the Ki-67-positive cells in the DG were located in clusters mainly in the subgranular zone (SGZ) adjacent to the hilus (Fig. 2A). DCX-labeled cells were observed mainly in the SGZ, which borders the granule cell layer (GCL), in the DG of the hippocampus (Fig. 3A).

For the Ki-67-positive cells in the DG of the total hippocampus, two-way factorial ANOVA indicated two significant effects, stress ($F_{1,\ 19} = 6.759$, $p = 0.0176$) and drug ($F_{1,\ 19} = 5.672$, $p = 0.0283$; Fig. 2B *right hand side*). For the DCX-positive cells in the total hippocampus, two-way factorial ANOVA indicated two significant effects, stress ($F_{1,\ 19} = 14.191$, $p < 0.01$) and drug ($F_{1,\ 19} = 13.700$, $p < 0.01$; Fig. 3B *right hand side*).

A separate analysis was conducted on the dorsal and ventral parts of the DG, with the number of Ki-67 and DCX-positive cells in the SGZ expressed per volume of corresponding DG. For the Ki-67-positive cells in dorsal hippocampus, two-way factorial ANOVA revealed a significant effect of quetiapine treatment ($F_{1,\ 19} = 7.388$, $p = 0.0136$; Fig. 2B *left hand side*). For the DCX-positive cells in dorsal hippocampus, two-way factorial ANOVA revealed significant effects of quetiapine treatment ($F_{1,\ 19} = 11.036$, $p < 0.01$) and stress ($F_{1,\ 19} = 5.812$, $p = 0.0262$; Fig. 3B *left hand side*). In contrast, no significant effect of quetiapine treatment × stress interaction was found.

In the ventral hippocampus, two-way ANOVA revealed a significant major effect of stress for the Ki-67-positive cells ($F_{1,\ 19} = 13.688$, $p < 0.01$; Fig. 2B *middle*) and for the DCX-positive cells ($F_{1,\ 19} = 10.148$, $p < 0.01$; Fig. 3B *middle*). Similar to dorsal subregion, no significant effect of quetiapine treatment × stress interaction was found.

3.2. Novelty Suppressed Feeding (NSF) test

The effects of intermittent social defeat and chronic QTP treatment in the NSF test were examined one day after the last injection. The Kruskal-Wallis test revealed a significant difference in the latency in the NSF test ($H_{3,\ 21} = 12.194$, $p < 0.01$; Fig. 4A). Mann-Whitney comparisons showed significant differences between the *Control* and *Stress* groups ($p < 0.05$) and between the *Quetiapine + Control* and *Quetiapine + Stress* groups ($p < 0.05$). However, no significant effect of QTP treatment on latency in the NSF test was found. Also, the Kaplan-Meier survival analysis showed that latency was significantly increased in the stressed animals, independent of QTP treatment (Kaplan–Meier survival analysis, Mantel-Cox log-rank test, $p < 0.01$; Fig. 4B). As proxy data for the appetite drive, Table 1 indicates that no significant differences were observed in cumulative food intake during the 28-days administration of QTP.

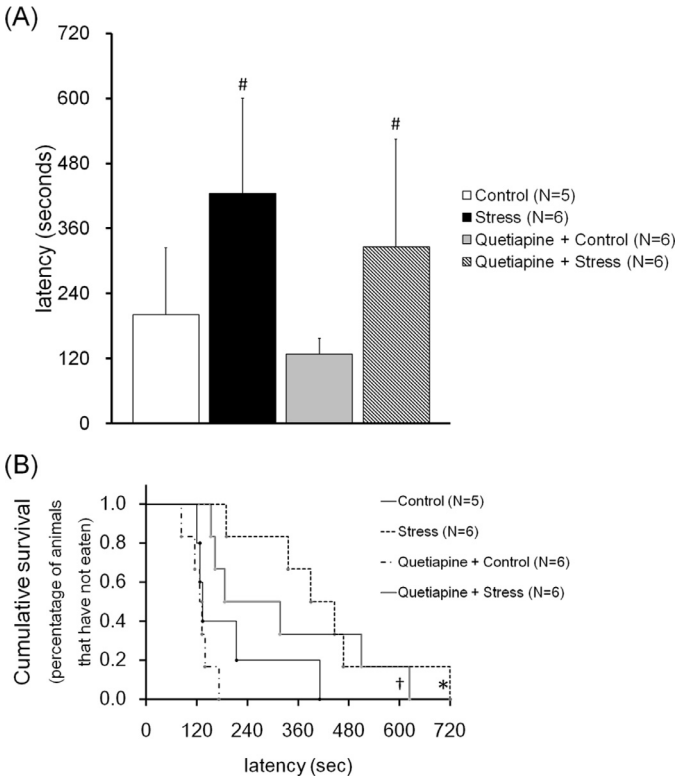

Fig. 4. Effects of intermittent social defeat and chronic quetiapine treatment on the time to feeding (latency) in a Novelty-Suppressed Feeding (NSF) test. The results are expressed as the mean latency to feeding in seconds (A) or as the cumulative survival of animals that have not eaten for over 12 min (B). The exposure to psychosocial stress significantly increased the latency to feeding, while no effect of chronic quetiapine treatment was observed. * $p < 0.05$ (Kaplan-Meier survival analysis, Mantel-Cox log-rank test), # $p < 0.05$ (v.s. control group treated with matching drugs).

4. Discussion

The present study indicates a novel finding that chronic administration with QTP stimulates the cell proliferation and generation of neuroblasts/immature neurons of dorsal hippocampus independent of stress exposure. Several studies have indicated that there are substantial differences in the effects of stress exposure and psychotropic drugs on adult neurogenesis across the transverse axis of the hippocampal DG (Alves et al., 2018; Banasr et al., 2006; Jayatissa et al., 2006; Tanti et al., 2012; Zhou et al., 2016). And a large body of evidence indicates that the dorsal hippocampus is involved in learning, memory and spatial navigation, while the ventral part is linked to emotional behavior and regulation of the neuroendocrine stress axis (Moser and Moser, 1998; Sahay and Hen, 2007). Thus, a QTP-induced increase in dorsal hippocampal proliferation and immature neurons may contribute to the improvement of cognitive function. Indeed, several studies reported that chronic administration of QTP results in an increase in the cognitive performance of rodents (Amin et al., 2014; Luo et al., 2014; Nikiforuk, 2013) and in the alleviation of cognitive deficit in schizophrenic patients (Désaméricq et al., 2014; Keefe et al., 2007; Wang et al., 2013). Many previous studies have demonstrated that chronic treatment of atypical antipsychotics including QTP, leads to the increases in cell proliferation, survival, and neurogenesis in the total hippocampal DG (Chen et al., 2013; Chikama et al., 2017; Halim et al., 2004; Kodama et al., 2004; Luo et al., 2005; Morais et al., 2017; Wakade et al., 2002; Xu et al., 2006; Xue et al., 2017). As far as we know, this is the first study to show the regional differences in positive effects of atypical antipsychotics on cell proliferation and neuroblasts/immature neurons between dorsal and ventral hippocampus. Although Ki-67 and DCX have been utilized as reliable quantitative markers of proliferating cells and neuroblasts/immature neurons, respectively (Couillard-Despres et al., 2005; Rao and Shetty, 2004; von Bohlen und Halbach, 2011), the stage-specific effect of QTP on hippocampal neurogenesis remains unknown. Because DCX expression extends from the proliferation stage to the period of postmitotic maturation, it would be interesting to distinguish the DCX-positive populations of precursor cells from neuroblasts/immature neurons. Thus, in order to dissect the mechanisms through which quetiapine may be acting, future studies will be done to determine the populations of Ki-67 + /DCX + and Ki-67 − /DCX + cells using a double-staining technique. And further studies will be needed that use an exogenous application of bromodeoxyuridine (BrdU) followed by a long-term chase to observe the formation of new neurons using co-localization with a marker for mature neurons.

It is still unclear that the mechanism underlying chronic administration with QTP preferentially stimulates cell proliferation and neuroblasts/immature neurons of dorsal hippocampal SGZ. Concerning the differential effects of psychotropic drugs on hippocampal neurogenesis across the dorso-ventral axis, previous studies indicated that the selective serotonin reuptake inhibitors (SSRIs, such as fluoxetine or escitalopram) and agomelatine (acting as an antagonist of 5-HT2C receptor and agonist of melatonergic receptors 1 and 2), preferentially stimulated adult neurogenesis in the ventral hippocampus, which suggests that the ventral hippocampus is more vulnerable to the changes in serotonergic neurotransmission than is the dorsal part (Banasr et al., 2006; Jayatissa et al., 2006; Tanti et al., 2012; Zhou et al., 2016). We speculate that two mechanisms may be responsible for the dorsal specificity of QTP. One is that chronic QTP treatment increases the release of norepinephrine in dorsal hippocampus mediated by the neuronal activation of locus coeruleus (LC). The LC is a dense cluster of noradrenergic neurons which project to wide areas of the brain involved in arousal and stress response (Benarroch, 2009), and the somatodendritic α_2-adrenergic receptors in the LC exert an inhibitory modulation on the release of norepinephrine in terminal areas (Fernández-Pastor and Meana, 2002; Mateo and Meana, 1999; Mateo et al., 1998). Parini et al. (2005) indicated that systemic treatment of clonidine, an α_2-adrenoceptor agonist, reduced the release of norepinephrine in dorsal hippocampus. And Yamamura et al. (2009) reported that intraperitoneal injection of QTP which has inhibitory effects on α_2-adrenergic receptors, increased extracellular levels of norepinephrine in the medial prefrontal cortex of free moving rats. Thus, these findings suggest that chronic administration with QTP induced the increase in release of norepinephrine in dorsal hippocampus via the blockade of α_2-adrenergic receptors in the LC, which may contribute to the preferential stimulation of dorsal hippocampal neurogenesis. Indeed, two previous studies indicated that chronic treatment of reboxetine, a selective norepinephrine reuptake inhibitor, increases adult hippocampal neurogenesis (Malberg et al., 2000; Meneghini et al., 2014).

Another candidate is that a cell cycle-associated molecule, p21/Cdkn (cyclin-dependent kinase inhibitor)1a. Kondo et al. (2013) reported that chronic administration with QTP leads to downregulation of p21/Cdkn1a gene transcript, in the postmitotic neurons. Of interest, in

Table 1
Cumulative food intake over 28-days under stress exposure and quetiapine treatment.

	Control ($N = 5$)	Stress ($N = 6$)	Quetiapine + Control ($N = 6$)	Quetiapine + Stress ($N = 6$)
Cumulative food intake (g per 28-days)	638.8 ± 69.1	632.8 ± 49.9	623.4 ± 40.9	622.5 ± 33.8

the p21 knockout mice, increased neurogenesis was observed in the dorsal hippocampus, but not in the ventral subregion (Scholpa et al., 2016). In order to elucidate the cell cycle-specific effects of QTP on dorsal hippocampal neurogenesis, further studies will need to be conducted.

On the other hand, in the ventral area, hippocampal cell proliferation and immature neurons were negatively affected by psychosocial stress, but little effect has been observed under QTP treatment. Previous studies indicated that chronic administration with QTP blocked the suppression of cell proliferation, differentiation, and survival of the hippocampus induced by repeated restraint stress (Luo et al., 2005; Xu et al., 2006). Although the present results are not consistent with these previous data, this inconsistency may be attributed to the separate analysis of dorsal and ventral hippocampal subregion. In fact, we found that chronic QTP treatment apparently blocked the stress-induced decrease in cell proliferation and generation of neuroblasts/immature neurons of the total hippocampus. However, given that ventral hippocampal neurogenesis plays an important role in the modulation of an antidepressant effect (O'Leary and Cryan, 2014; Tanti and Belzung, 2013), the present data showing little effect of QTP on ventral hippocampal proliferation and immature neurons seem to be inconsistent with preclinical data that QTP has a putative antidepressant property (Ignácio et al., 2018; Kotagale et al., 2013; Orsetti et al., 2007).

Indeed, the present study indicated that chronic QTP treatment does not affect the stress-induced increase in latency to consume a food pellet in the NSF test. Because the NSF test is a hyponeophagia-based paradigm that measures an anxiety-related behavior that is sensitive to chronic antidepressant treatment, it has been suggested that this behavioral test is a useful tool for screening for novel candidate antidepressants (Bodnoff et al., 1989; David et al., 2010; Dulawa and Hen, 2005; Santarelli et al., 2003). Several studies have suggested that latency in the NSF test is causally dependent on changes in hippocampal neurogenesis (David et al., 2009; Deng and Gage, 2015; Mateus-Pinheiro et al., 2013; Wu and Hen, 2014). In a study with selective ablations of neurogenesis in the dorsal and/or ventral DG using a focal x-irradiation, Wu and Hen (2014) indicated that immature neurons in the ventral hippocampus are necessary for a positive effect of fluoxetine on latency in the NSF test. And Morais et al. (2017) have demonstrated that the improvement of hippocampal neuroplasticity induced by chronic administration of clozapine is involved in the positive modulations of mood, anxiety, and cognition assessed by a battery of behavioral tests. Thus, it seems to be reasonable to make the interpretation that an absence of a blocking effect by chronic treatment with QTP on ventral hippocampal neurogenesis is associated with an absence of an alleviating effect of QTP on stress-induced behavioral abnormality. While, Snyder et al. (2011) reported that transgenic mice with a conditional ablation of hippocampal neurogenesis showed a normal anxious phenotype, assessed by the NSF test, which suggests that some changes of hippocampal neurogenesis may be rather an epiphenomenon than a therapeutic efficacy. Future studies with additional behavioral tests should be done to elucidate the relation between the neurogenic effect and behavior-modulating effect of QTP.

Although QTP exerts broad therapeutic potential in clinical settings (Altamura et al., 2003; Calabrese et al., 2005; Cutler et al., 2009; Ignácio et al., 2018; Maneeton et al., 2012; McIntyre et al., 2009; Sanford and Keating, 2012; Suttajit et al., 2014; Weisler et al., 2009, 2012), the present findings indicate that stress-induced hyponeophagic behavior is not affected by chronic treatment with QTP. This discrepancy may be explained by the differences in the pharmacological profiles between QTP and its metabolite. *N*-desalkyl quetiapine, also known as norquetiapine, which has been identified as a major active metabolite of QTP in humans, has inhibiting potency for the norepinephrine transporter (NET) and partial agonist activity at 5-HT_{1A} receptors (Jensen et al., 2008). Considering that NET inhibition and 5-HT_{1A} receptor agonism are strongly related to the action mechanism of antidepressants and anxiolytics, the unique pharmacological profile of norquetiapine provides a mechanistic basis for the antidepressant- and anxiolytic-like activities of QTP treatment. Therefore, the broad therapeutic range of QTP for neuropsychiatric disorders may be attributed to the combination of the antipsychotic action of QTP and the antidepressive/anti-anxiety actions of norquetiapine. However, in rodents, the production of norquetiapine from QTP is considerably lower than in humans, when treated intraperitoneally or subcutaneously (Hudzik et al., 2008). Recently, Cross et al. (2016) indicated that both QTP and norquetiapine exhibit an anxiolytic-like effect in the punish-responding test, while the depression-like behaviors seen in the forced swim and learned helplessness tests are blocked by norquetiapine, but not by QTP. In the present study, we adopted intraperitoneal injection of QTP as the administration route, which may have led to minimal production of norquetiapine and less antidepressant potential than for the concomitant effect of QTP and norquetiapine observed in clinical settings. Thus, future study will be necessary to clarify if chronic administration of norquetiapine stimulates ventral hippocampal neurogenesis and exerts an antidepressant effect.

Concerning the effects of antipsychotics on adult neurogenesis in other than hippocampal DG, chronic treatment with atypical antipsychotics increased adult neurogenesis in the SVZ (Lasut et al., 2018; Nasrallah et al., 2010; Wakade et al., 2002). The progenitor cells generated in the SVZ travel through the rostral migratory stream and differentiate into new neurons in the olfactory bulb, which indicates that neurogenesis in the SVZ is required for olfactory behavior (Alvarez-Buylla and Garcia-Verdugo, 2002; Sakamoto et al., 2014). Of interest, a previous study by Inta et al. (2012) suggested that increased neurogenesis in the SVZ may alleviate symptoms of schizophrenia via the modulation of dopaminergic signaling at neural stem cells. On the other hand, for adult neurogenesis in the hypothalamus, Rojczyk et al. (2015) reported that Ki-67-positive cells were increased by chronic administration with olanzapine, chlorpromazine and haloperidol, while DCX-positive cells were increased by chlorpromazine and decreased by haloperidol. Given that hypothalamic neurogenesis is involved in energy balance control (Pierce and Xu, 2010), the alterations of hypothalamic neurogenesis induced by antipsychotic agents may result in body weight gain, one of the major side effects. Taken together, further study assessing the effects of chronic QTP treatment on adult neurogenesis in the SVZ and hypothalamus may clarify the clinical significance of QTP, from the standpoints of potential therapeutic effect and prevention of adverse drug reactions.

Our study has several limitations, including the experimental protocol and small sample size. Of note, our animals were continuously pretreated with the drug before the start of intermittent stress exposure. It is possible that the data obtained through this study design implies a preventive effect of chronic administration of QTP on stress-induced changes, rather than a therapeutic effect. Because a very low number of animals were included in the present study, it is possible that the individual differences in susceptibility to the effects of stress exposure and treatment with QTP could be attributed to the large variations of behavioral data. In order to ensure sufficient statistical power and to clarify the therapeutic potential of QTP, further study will be required with a larger sample size and a better experimental design in which stress is given before the vehicle or QTP administration. In addition, appetite drive was not measured in the present study. Because the neophobic behavior in the NSF test relies on food consumption, the effects of QTP on feeding behavior could be involved in the data obtained in the NSF test. A recent review by Benarroch et al. (2016) indicated that atypical antipsychotics induced weight gain through changes in the appetite and feeding behaviors of humans. However, in rodents, increases in cumulative food intake are mainly observed in females treated with atypical antipsychotics (Benarroch et al., 2016). In the present study, the cumulative food intake during 28-days administration of QTP of the four experimental groups was not significantly changed. This supplementary data may support that our interpretation of the results obtained in the NSF test is valid, however, the effects of

psychosocial stress and chronic treatment with QTP on the appetite drive and motivational aspects of food intake should be addressed in future studies.

In conclusion, the present study indicates that chronic QTP treatment has a neurogenic effect preferentially in the dorsal DG; however, positive effects of QTP on ventral hippocampal neurogenesis and anxiety-related behavior were not observed.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Supplementary materials

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