Intracerebroventricular infusion of cytosine-arabinoside causes prepulse inhibition disruption

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Adult neurogenesis in hippocampus is associated with behaviors such as learning. Hippocampus is involved in the regulation of prepulse inhibition (PPI), but the relationship between neurogenesis and PPI is unexplored. We conducted four experiments to determine the role of neural progenitor cell proliferation in PPI. Intracerebroventricular infusion of cytostatic cytosine arabinoside caused PPI disruption but repeated exposure to PPI sessions prevented the PPI disruption. Corticosterone treatment, which decreases hippocampal cell proliferation, caused PPI disruption, whereas antidepressant and exercise, which increased cell proliferation, did not affect PPI. These results suggest that cell proliferation is involved in the first encounter with PPI test while its importance may decrease upon repeated exposures to the tests. ***NeuroReport***

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Introduction

Continuous adult neurogenesis is predominant in the dentate gyrus of the hippocampus [1,2]. Previous reports showed the association of neurogenesis and certain behaviors (for instance, memory formation [3], mating [4], and fear conditioning [5]), and the essential roles of neurogenesis in regulation of these behaviors [4,5]. Recently, it is found that certain psychiatric medications including antidepressants and antipsychotics upregulate neurogenesis [6,7]. It is hypothesized that altered neurogenesis may contribute to the etiology of psychiatric disorders and psychiatric medications may exert their effects through upregulation of neurogenesis [7,8].

Apart from memory, hippocampus modulates sensorimotor processes and prepulse inhibition (PPI) [8]. PPI, which refers to the reduction of startle reflex by a weak prepulse 30–500 ms before the startle stimulus, is thought to represent sensorimotor-gating mechanisms protecting the processing of prepulse by attenuating the response to startle stimulus [8]. Until now, there is a lack of information showing the relationship between hippocampal neurogenesis and PPI. As neurogenesis involves cell proliferation, migration, and maturation, here we show the involvement of cell proliferation in PPI through four experiments.

In experiment 1, intracerebroventricular infusion of a cytostatic agent, cytosine arabinoside (Ara-c) was used to inhibit cell proliferation in rat hippocampus and subventricular zone (SVZ). This treatment caused PPI disruption in animals that had no previous PPI test. Experiment 2 tested whether repeated exposure to PPI prevents Ara-c-induced PPI disruption. Experiment 3 aimed at elucidating whether newborn cells are required for PPI improvement over repeated exposures. Experiment 4 investigated effect of different treatment modalities, which affects hippocampal cell proliferation, on PPI. Treatment schedules are depicted in Fig. 1. Ara-c infusion inhibited both hippocampus and SVZ cell proliferation and therefore it could not differentiate whether the results are consequence of inhibition in which region. However, as other reports stated the importance of hippocampus in PPI regulation it is more likely that the altered PPI is the result of hippocampal cell proliferation inhibition.

Methods

Animals and cytosine arabinoside treatment

Adult male Sprague–Dawley rats (260–290 g) were obtained from the Laboratory Animal Unit, The University of Hong Kong. Animals were kept in groups of three under constant temperature (23 ± 2°C) and 12-h light/dark cycle and fed *ad libitum*. Intracerebroventricular infusion of Ara-c was conducted as described previously [4]. In brief, animals were implanted with osmotic pumps (1007D, Alzet, Palo Alto, California, USA) filled with either *2%* Ara-c (Calbiochem, San Diego, California, USA) or physiological saline (as control). Pumps were implanted subcutaneously at the dorsal neck region and

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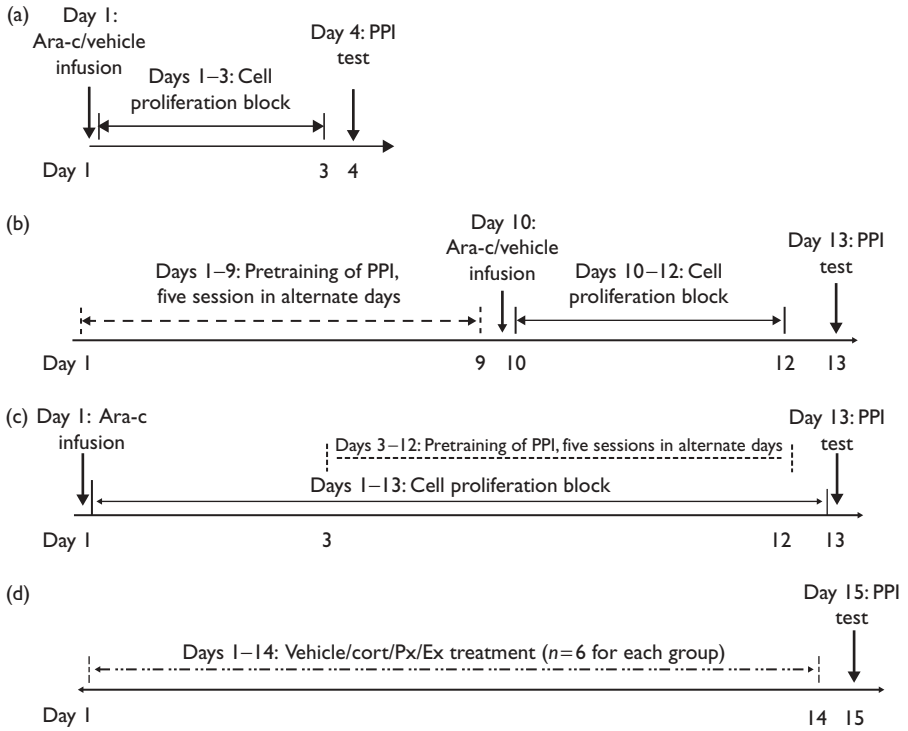
Fig. 1



Schedules of experiments. (a) Schedule of experiment 1: cytosine arabinoside (Ara-c) or vehicle infusion of prepulse inhibition (PPI) test-naive rats started on day 1 and continued for 3 days. PPI test was then carried out on day 4. (b) Schedule of experiment 2: test-naive animals were subjected to PPI sessions from day 1 to 9 on alternate days. On day 10, osmotic pumps with either Ara-c or saline (as control) were implanted. The cell proliferation inhibition was maintained for 3 days and then the animals were subjected to PPI test. (c) Schedule of experiment 3: 'neurogenesis inhibition – repeated exposure of PPI – PPI testing' determined whether increase in PPI during testing is because of adaptive changes of preexisting circuit or cell proliferation. (d) Schedule of experiment 4: animals received vehicle, corticosterone, paroxetine (Px), or exercise (Ex) treatment for 14 days and then were subjected to PPI test.

connected to a cannula, which was placed 1 mm posterior and 1.5 mm lateral to bregma. Experimental procedures were approved by Committee on the Use of Live Animals in Teaching and Research, The University of Hong Kong.

Prepulse inhibition apparatus and procedures

For PPI test, two acoustic startle chambers were used (SR-LAB, San Diego Instruments, San Diego, California, USA). Each isolation chamber contained a nonrestrictive cylindrical enclosure and a loudspeaker above the enclosure. The background noise was maintained at 65 dB. For each startle reflex, signals were taken at 1.0 ms intervals and in total 100 readings were taken from the onset of the startle stimulus in pulse-alone trials and the onset of the prepulse in prepulse+pulse trials. The average value of the startle response was used to determine the startle reactivity.

In the PPI test, animals were presented with four types of trials: (i) pulse-alone; (ii) prepulse-alone; (iii) prepulse+pulse (PPI), and (iv) no stimulus. PPI is the reduction of magnitude in prepulse+pulse trials relative to that in pulse-alone trials. The magnitude of pulse is 120 dB (lasted for 40 ms), whereas prepulses (lasted for 20 ms) are set at four magnitudes: 69, 73, 77, and 81 dB.

After 2 min of acclimation in cylinders, six pulse-alone stimuli were presented to stabilize startle responses. Eight blocks of discrete trials were then presented. Each block consisted two pulse-alone (120 dB), four prepulse-alone (69, 73, 77, and 81 dB respectively), four prepulse+pulse (with four different prepulse magnitudes), and one no stimulus trial. Eleven trials were arranged in a pseudorandom order with intertrial intervals ranging from 10 to 20 ms.

Repeated prepulse inhibition training

For experiment 2, test-naive animals received PPI test on alternate days from day 1 to 9, then with Ara-c infusion from day 10 to 13. The last PPI test was carried out on day 13. For experiment 3, Ara-c infusion was maintained throughout the 13-day period and five PPI tests were carried out from day 3 to 12. The last PPI test was carried out on day 13 (Fig. 1b and c).

Drug treatments and exercise training

Animals were divided into four groups and received the following treatments for 14 days: (i) corticosterone treatment (40 mg/kg, subcutaneous injection); (ii) paroxetine treatment (10 mg/kg, intraperitoneal injection); (iii) exercise training: free access to running wheel (with 0.8 ml sesame oil subcutaneous injection as vehicle); and (iv) vehicle (sesame oil)-treated control group. The dosage of drugs was shown to be effective in suppressing/increasing neurogenesis [9,10]. Twenty-four hours after the last dose of drug delivery, the animals were subjected to PPI test.

Bromodeoxyuridine labeling and staining

Bromodeoxyuridine (BrdU, 50 mg/kg, Sigma, St. Louis, Missouri, USA) was administered to animals, 7 and 1 h before they were killed. BrdU immunostaining was performed as described before [11].

Bromodeoxyuridine cell quantification

Brain sections from the hemisphere ipsilateral to infusion site were used for quantification under a 20 × objective. In SVZ, sections from 1800 μm anterior to bregma to 300 μm posterior to bregma were used. Four 40 μm eosin-counterstained sections were counted from each animal. In hippocampus, sections from 2200 μm posterior to bregma to 4800 μm posterior to bregma were used for quantification. Five eosin-counterstained sections from each animal were taken for quantitation in blinded manner.

Data analysis

PPI was calculated by determining the change in percentage between the mean value of pulse-alone trials and prepulse+pulse trials [i.e. percentage PPI (%PPI)= (mean of pulse-alone − mean of prepulse+pulse)/pulse alone × 100%]. Analysis among drug treatment groups were performed with analysis of variance (ANOVA) and least significant difference post-hoc test. Statistical significance was indicated by a P value of less than 0.05.

Results

As reported by others, no gross behavioral abnormality is observed in Ara-c-infused animals [4,12]. BrdU staining and cell quantification revealed that Ara-c-infused animals had significantly less BrdU-labeled cells in dentate gyrus and SVZ (Fig. 2), which confirms the effectiveness of Ara-c infusion.

Experiment 1

Percentage decreases on startle response (PPI) of saline-infused and Ara-c-infused animals are shown in Fig. 3a. All prepulses with different magnitudes (69, 73, 77, 81 dB) elicited PPI in saline-infused animals (69 dB: 20.70 ± 1.41%; 73 dB: 23.10 ± 3.53%; 77 dB: 28.72 ± 3.59%; and 81 dB: 40.25 ± 3.25%). The amount of PPI increased with the increase in prepulse intensity. When compared with saline-infused group, animals with Ara-c infusion showed lower percentage inhibition (disruption in PPI) (69 dB: 2.42 ± 4.57%; 73 dB: 6.22 ± 4.54%; 77 dB: 16.76 ± 3.78%; and 81 dB: 31.14 ± 4.64%) and significant differences between two groups were found when prepulse magnitudes were at 69, 73, and 77 dB (69 dB: $P < 0.01$; 73 and 77 dB: $P < 0.05$, Student's t-test). Percentage PPI of Ara-c group also increased with prepulse intensity, and there was no significant difference found between the two groups when prepulse was at 81 dB ($P=0.16$). No significant difference was found between startle amplitude (in arbitrary unit) between the two groups (saline-infused group=99.1 ± 28.8; Ara-c-infused group= 103.2 ± 8.2, $P=0.85$, values expressed in mean ± SEM).

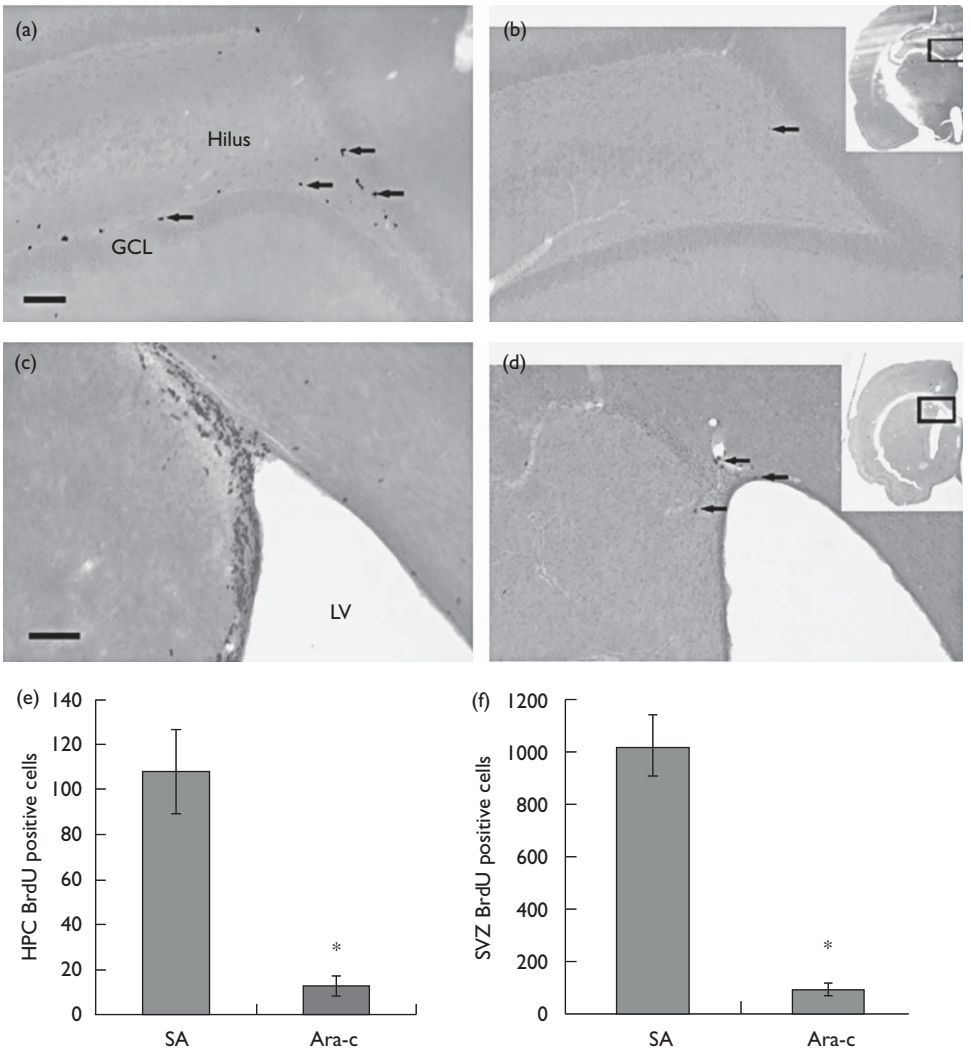
Experiment 2

This experiment examined our hypothesis that new cells are used as substrates for the establishment of PPI circuitry. We used an 'exposure – cell proliferation inhibition – testing' protocol for this (schedule described in Fig. 1b). Animals were exposed to multiple PPI sessions before the start of blocking cell proliferation. After training for five PPI sessions within 9 days, Ara-c infusion started and maintained for 3 days. Results of repeated PPI sessions are shown in Fig. 3b. In general, PPI showed a trend of increase over the training period in all prepulse intensities. Increase in PPI, because of their experience, was reported by other groups previously [13]. Then the animals were subjected to PPI test and the results are depicted in Fig. 3c. In contrast to results from test-naive animals, there was no significant difference found between saline-infused animals and Ara-c-infused animals at any prepulse magnitude levels (control animals: 69 dB: 35.70 ± 3.38%; 73 dB: 36.76 ± 7.44%; 77 dB: 41.32 ± 6.23%; and 81 dB: 52.32 ± 5.99%. Ara-c animals: 69 dB: 31.16 ± 2.85%; 73 dB: 32.71 ± 2.48%; 77 dB: 39.10 ± 4.39%; and 81 dB: 50.14 ± 3.03%. $P > 0.05$ for all comparisons between control and Ara-c groups at same prepulse level). The result suggests that blockage of cell proliferation affects PPI in test-naive animals, whereas no such observation could be found in animals with exposure to PPI before Ara-c infusion. No significant difference in startle amplitude was found between saline-infused and Ara-c-infused rats. (saline-infused group=139.4 ± 20.7; Ara-c infused group=133.7 ± 26.7, $P=0.87$, values expressed in mean ± SEM).

Experiment 3

This experiment determined whether increase in %PPI across training is dependent on changes of existing circuit or new cells (Fig. 1c). If new cells were essential for increase of %PPI across the training sessions, blocking cell proliferation throughout the process will abolish the increase. Three days after start of Ara-c infusion, animals were subjected to five training sessions as in experiment 2 and then the PPI test. Result of the PPI test on day 13 is shown in Fig. 3d. No significant difference could be found between saline-infused group and Ara-c-infused group at any prepulse level (control animals: 69 dB:

Fig. 2



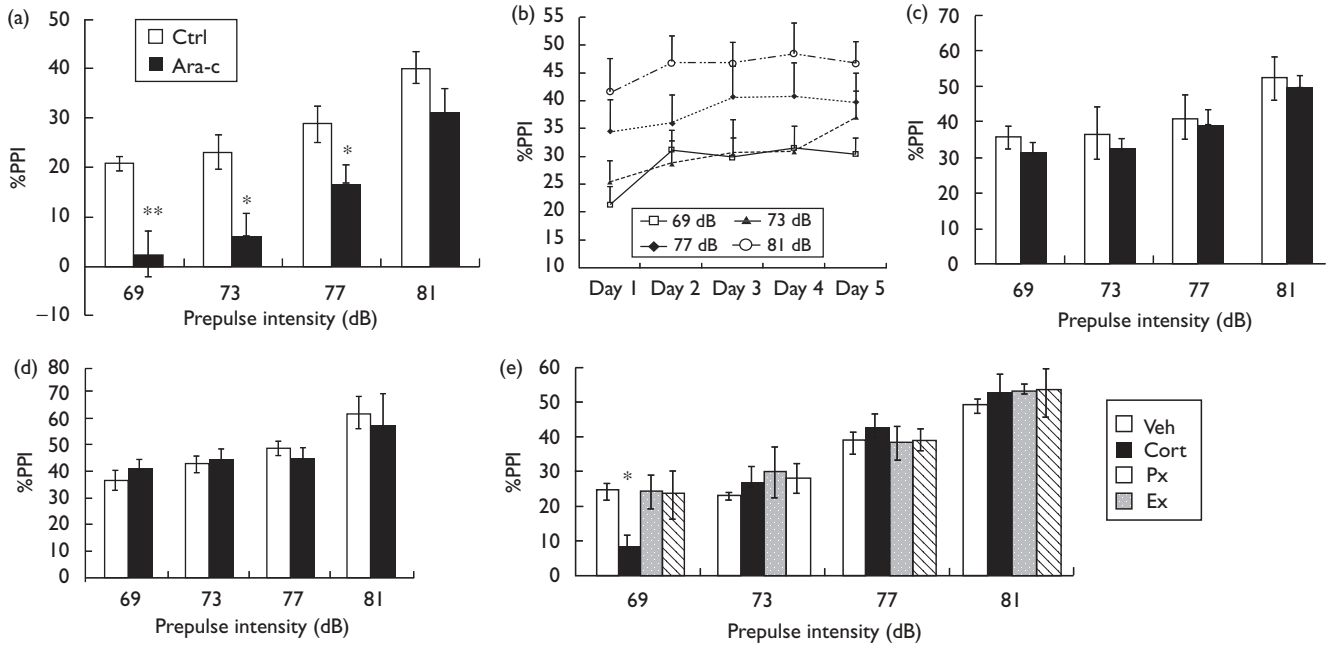
Cytosine arabinoside (Ara-c) infusion decreases bromodeoxyuridine (BrdU)-labeled cells in the hippocampus (HPC) and subventricular zone (SVZ). Locations of areas are indicated by open rectangles in the small thumbnail. Saline-infused (SA) animals (a and c) had significantly greater number of BrdU-labeled cells (indicated by arrows) in HPC (a) and SVZ (c) than Ara-c-infused animals (b and d). Scale bar = 100 μm. (e) Quantification of BrdU-immunoreactive cells in HPC. Significant difference in HPC BrdU-immunoreactive cells was found between saline and Ara-c treatment groups (SA: 107.8 ± 13.4; Ara-c: 12.8 ± 4.5; *$P < 0.001$, $n = 6$ for SA groups and $n = 9$ for Ara-c group). (f) Quantification of BrdU-immunoreactive cells in SVZ. SA animals had significantly higher cell number (1022.3 ± 115.5) than Ara-c treatment groups (92.1 ± 72.5; *$P < 0.0001$; $n = 6$ for SA group and $n = 9$ for Ara-c group). GCL, granule cell layer; LV, lateral ventricle. Scale bar: 100 μm.

36.64 ± 3.60%; 73 dB: 42.49 ± 2.91%; 77 dB: 48.57 ± 2.77%; and 81 dB: 61.96 ± 5.54%. Ara-c animals: 69 dB: 40.44 ± 3.92%; 73 dB: 43.64 ± 4.47%; 77 dB: 44.33 ± 4.67%; and 81 dB: 57.08 ± 11.61%. $P > 0.05$ for all inter-group comparisons, ANOVA). This result indicated that abolishment of new cell proliferation for 13 days do not prevent the increase in %PPI during repeated exposure.

Experiment 4

Three treatment modalities were used to determine the relationship between cell proliferation and PPI disruption (Fig. 1d). Chronic, high dose of corticosterone was shown to inhibit cell proliferation [9], whereas paroxetine (a selective serotonin reuptake inhibitor) and exercise increase cell proliferation [6,10]. The corresponding effects were confirmed by proliferation assay (Table 1), that is, corticosterone suppressed, whereas paroxetine and exercise increased cell proliferation. We expected that corticosterone treatment disrupts PPI and paroxetine treatment/exercise facilitate PPI. After treatments for 14 days, the animals were subjected to PPI test. At prepulse level 69 dB, corticosterone-treated animals showed significantly lower %PPI than vehicle-treated, paroxetine-treated, and exercised animals (controls: 24.10 ± 2.22%; corticosterone: 8.35 ± 2.79%; paroxetine: 24.24 ± 4.93%; exercise: 23.22 ± 6.85%. One-way ANO-

Fig. 3



Percentage prepulse inhibition (%PPI) in the three experiments. (a) Prepulse inhibition between saline-infused animals (control, $n=7$) and cytosine arabinoside (Ara-c)-infused animals (Ara-c, $n=10$). Results are expressed in mean percentage of inhibition ± SEM. When prepulse intensity is increasing, the %PPI increases in both groups. Significant difference between control and Ara-c groups were found at prepulse magnitude 69 dB (**$P<0.01$), 73 and 77 dB (*$P<0.05$). No significant difference is found at 81 dB. (b) Percentage of PPI change during 5 days of repeated PPI sessions. Prepulses are presented in four varying magnitudes, that is, 69, 73, 77, and 81 dB. Prepulses were delivered 40 ms before startle pulse (120 dB). Results are expressed in mean ± SEM. Over the training period, increase in %PPI is observed in all prepulse intensities. (c) PPI between saline-infused animals (control, $n=10$) and Ara-c-infused animals (Ara-c, $n=10$), with previous exposure to PPI sessions before infusion. Results are expressed in mean percentage of inhibition ± SEM. Percentage PPI increases in both groups with increasing prepulse intensity. No significant difference between control and Ara-c groups at the same prepulse level is found ($P>0.05$ at all prepulse levels, Student's *t*-test). (d) Repeated PPI training after cell proliferation blocking reversed PPI disruption. Animals received Ara-c treatment, five repeated PPI sessions, and finally the PPI test. No significant difference between vehicle or Ara-c groups was found. Results are expressed in mean percentage of inhibition ± SEM [$P>0.05$, analysis of variance (ANOVA)]. (e) Effect of subchronic corticosterone (Cort), paroxetine (Px), and exercise (Ex) on prepulse inhibition. The results are shown in percentage of inhibition. At prepulse level 69 dB, Cort group shows a significantly lower %PPI than vehicle-treated, Px, and Ex training (*$P<0.05$, ANOVA with least significant difference post-hoc test. $N=6$, each group) groups. When prepulse intensity is equal to or greater than 73, there is no significant difference found.

Table 1 Number of proliferative cells in dentate gyrus after treatments for 2 weeks

Treatment	Number of BrdU-labeled cells ± SEM
Control/vehicle	176 ± 16.67*
Corticosterone	93 ± 13.95*
Paroxetine	262.75 ± 16.41**
Exercise	295.2 ± 45.09**

BrdU, bromodeoxyuridine.
*$P<0.05$, significant difference with the other three groups. Analysis of variance (ANOVA), least significant difference (LSD) post-hoc test. $N=6$, for each group.
**$P<0.05$, significant difference with vehicle and corticosterone groups, ANOVA, LSD post-hoc test.

VA, $P<0.05$) (Fig. 3e). No significant difference was found among the other three groups. When the prepulse magnitudes were above 73 (i.e. 73, 77, and 81 dB), no significant difference was found between any groups. Regression analysis was performed to determine possible correlation between BrdU-labeled cell number and %PPI at 69 dB, but no significant correlation was found ($R^2=0.004$, $P=0.784$).

Discussion

Neurogenesis is involved in various physiological functions, including memory formation, female mate selection, and the therapeutic effect of antidepressants [3,4]. When neurogenesis is inhibited, the related functions will be disrupted (for instance, pheromone could not exert mate preference effect when neurogenesis was abolished [4]). Iwata *et al.* [14] reported that PPI disruption was found when hippocampal neurogenesis was blocked by irradiation. However, long recovery period (3 months) and potential side effects may affect the results. Ara-c treatment was shown to decrease dendritic complexity in hippocampus and may affect synaptic plasticity [15]. This may affect the test outcomes but it was shown that the drug did not affect memory performance in acute period. Thus, Ara-c infusion served as a less invasive method for cell proliferation blocking with the advantages of shorter recovery period and potentially fewer side effects.

Neurogenesis involves cell proliferation, migration, and maturation. This study shows the relationship between neural progenitor cell proliferation and PPI. When cell proliferation is blocked by Ara-c, PPI of test-naive animals was disrupted. Interestingly, when animals were exposed to PPI sessions repeatedly before cell proliferation blocking, no PPI disruption was found. As experience of PPI diminishes variability of PPI and facilitates PPI [13,16], it is possible that the experience stabilizes the circuitry regulating PPI before cell proliferation blocking. To further determine whether new cells are essential for PPI improvement, animals underwent cell proliferation blocking during repeated PPI training sessions. Although difference between Ara-c and control groups could be found at the first session (data not shown), there is no significant difference found between the control and Ara-c groups after the 5 sessions. These results from experiments 1 to 3 imply that blocking cell proliferation causes PPI disruption in the first encounter to PPI test. Repeated PPI exposure could prevent (shown in experiment 2) or reverse (experiment 3) the disruption.

It was shown that mice strains with higher neurogenesis levels did not show a better spatial memory performance after repeated training, but they showed better acquisition of spatial memory (i.e. learnt faster) [17]. This study agrees with the finding that when rats with blocked cell proliferation faced the first PPI test, PPI disruption occurred. After a few repeated exposures there is no disruption in Ara-c-treated animals. Thus, the presence of new cells may be important in 'acquisition' of PPI rather than affecting percentage of PPI after repeated exposures. Cell proliferation is one of the contributors involved in PPI demonstration, and its importance may lie on initial encounter with PPI test. Other factors such as mature cells, synaptic circuits, and neurotransmitters may have more important roles in PPI in later encounters with PPI.

What are the possible roles of newborn cells in PPI? One possibility is that newborn neurons integrate into existing circuit for functional outcome. It is shown that learning experience recruits new hippocampal neurons and enhances their long-term survival, which is a possible mechanism to retain trace memory [18]. However, as PPI could still be found even with ablation of cell proliferation (experiment 3) and a new progenitor cell takes about 4 weeks for maturing into functional neuron [19], it is unlikely that short-term ablation affects behavior through this mechanism. Another possibility is that new neural progenitors secrete neurotrophic factors, which promote neurite outgrowth and synaptic formation of mature neurons [20]. By acting this way the progenitor cells do not directly involve in circuitry formation but assist the existing neurons to form networks. This view may explain why acute ablation of cell proliferation for less than 7 days could induce behavior changes [4]. Further information is required to find out the role of new cells and relationship between neurogenesis and behavioral outcomes.

Corticosterone treatment, which suppresses cell proliferation [21,22], caused PPI disruption in test-naive animals. Although Ara-c infusion decreases cell proliferation by nearly 90% (Fig. 2), corticosterone treatment decreases cell proliferation to a lesser extent (approximately 32% decrease was reported [9]). The difference in cell proliferation inhibition may explain why PPI disruption of corticosterone-treated animals is not as obvious as in Ara-c-treated animals. In contrast, antidepressant treatment (paroxetine) and exercise enhance neurogenesis in central nervous system but did not show facilitation of PPI. Whether the formation of synaptic junction also plays a role in PPI disruption remains to be established. This suggests that neurogenesis is a necessary, but not sufficient condition for PPI.

This study could not differentiate whether the PPI disruption is caused by cell proliferation inhibition in hippocampus or in SVZ. However, as hippocampus was shown to be involved in sensorimotor gating [8] and neurons that arise from the SVZ mainly migrate to olfactory system, it is likely that the PPI disruption is related to hippocampal cell proliferation. Long-term inhibition may be used in future to study influence of neurogenesis. In patients suffering from schizophrenia, decreased hippocampal volume and neurogenesis are observed and this is associated with cognitive function deteriorations [23]. It is speculated that the decreased hippocampal neurogenesis is the common cause of cognitive disturbances, PPI disruption, and auditory hallucination [24].

Conclusion

This study indicates the role of new neural progenitors in initial encounter to PPI testing. Although repeated exposure to PPI tests reversed the initial disruption, importance of new cells may be limited to the first encounter. This study may provide insights for further studies about relative importance of cell proliferation, synaptic circuits, and preexisting neurons in PPI demonstration, and mechanism of positive symptoms, such as hallucination, in schizophrenia.

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