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Phosphodiesterase type 1 inhibition improves learning in rats exposed to alcohol during the third trimester equivalent of human gestation

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Abstract

Deficits in learning and memory have been extensively observed in animal models of fetal alcohol spectrum disorders (FASD). Here we use the Morris Maze to test whether Vinpocetine, a Phosphodiesterase type 1 inhibitor, restores learning performance in rats exposed to alcohol during the third trimester equivalent of human gestation. Long Evans rats received ethanol (5 g/Kg ip) or saline on alternate days from postnatal day (P) 4 to P10. Two weeks later (P25), the latency to find a hidden platform was evaluated (2 trials per day spaced at 40-min inter-trial intervals) during 4 consecutive days. Vinpocetine treatment started on the first day of behavioral testing: animals received vinpocetine (20 mg/kg ip) or vehicle solution every other day until the end of behavioral procedures. Early alcohol exposure significantly affected the performance to find the hidden platform. The average latency of ethanol exposed animals was significantly higher than that observed for the control group. Treatment of alcohol-exposed animals with vinpocetine restored their performance to control levels. Our results show that inhibition of PDE1 improves learning and memory deficits in rats early exposed to alcohol and provide evidence for the potential therapeutic use of vinpocetine in FASD.

Introduction

Fetal Alcohol Spectrum Disorders (FASD) is a general term used to describe the range of disabilities caused by prenatal exposure to alcohol. These effects may include hyperactivity [1], attention deficits [2], impaired visual processing [3;4], autistic behavior [5], and learning and memory deficits [6].

The Morris water maze has been widely used to investigate learning and memory in rodents [7]. Briefly, rodents learn to swim to a hidden escape-platform submerged in a circular pool filled with opaque water. Across several trials, learning is indicated by a decrease in the latency to find the platform. Several studies reported that rodents exposed to alcohol during the third trimester equivalent of human gestation show increased latencies to find the platform when compared to controls, indicating the presence of spatial learning and memory deficits [8;9]. Interestingly, children with FASD show similar learning impairments in a “virtual Morris water maze” [10].

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The Morris water maze test has also been used for the screening of drugs that could improve learning and memory in normal and pathological conditions [11;12]. An interesting group of these drugs are the phosphodiesterase (PDE) inhibitors. They have been shown to improve learning and memory in several species, including mice [13;14], rats [15;16] and humans [17;18]. The effects of PDE inhibitors have been attributed to an increase in cAMP levels, which in turn can activate the cyclic AMP response element binding protein (CREB) leading to expression of plasticity-related genes [13;17]. Recently, we showed that Vinpocetine, a PDE type 1 inhibitor, was able to restore ocular dominance plasticity (ODP) in the visual cortex of ferrets exposed to alcohol during the third trimester equivalent of human exposure [19]. ODP shares similar mechanisms with learning and memory, such as the dependence on CREB function [20]. Here we test whether vinpocetine treatment can improve Morris water maze performance in rats exposed to alcohol during the third trimester equivalent of human gestation.

Methods

Animal Treatment

All experimental procedures were approved by the IACUC. Twelve pregnant dams were purchased from Harlan Laboratories and offspring were used as experimental subjects. Animals were maintained on a 12:12h light/dark cycle with food and water ad libitum. The day of birth was considered postnatal day 0 (PD0). Litters were left undisturbed until PD4, when pups within the same litter were assigned to ethanol or saline treatment groups.

From PD4 to PD10, 56 rats were injected with 5g/Kg of ethanol (ip., 25% in saline) on alternate days. An equivalent volume of saline solution was injected in 45 rats. Treatment on alternate days was chosen since it mimics binge drinking in humans which is associated with severe cognitive and behavioral deficits [21–23].

At weaning (PD21) animals from the same litter were separated by sex and housed in groups of 2–3 rats by cage. From the initial sample of rats treated with ethanol (n= 56) or saline (n = 45), only 44 were used for the present study. The other 57 animals were used in other studies or died during the treatment. Thus, at PD25 and PD27, the ethanol-treated animals were randomly assigned within the litter to receive treatment with vinpocetine (20 mg/kg IP, VINP group, n=15, 8 females and 7 males) or vehicle solution (dimethylsulfoxide IP, ETOH group, n=14, 6 females and 8 males). Animals treated with saline also received vehicle solution (CONT group, n=15, 7 females and 8 males).

To minimize the influence of litter effects, multiple litters were used and often a litter had animals from our three groups: a) 6 litters had 1–2 animals from each group (saline-treated, ethanol-treated and ethanol-treated + vinpocetine), b) 3 litters had 1–2 animals from groups Ethanol-treated and Ethanol-treated + Vinpocetine, c) 2 litters had 1–2 animals from groups saline-treated and ethanol-treated, and d) 1 litter had 2 animals from the saline group.

Blood Ethanol Concentration

Blood was collected from a separate subset of subjects by heart puncture 1 or 3 hours after alcohol exposure. Blood was centrifuged at 4,000 rpm for 5 min and supernatant stored at -20° C. BEC was assessed using a commercial kit (333-A diagnostics kit; Sigma, St. Louis, MO).

Morris Water Maze

From PD25 to PD28, animals were tested daily in sessions between 13:00h and 16:00h. The maze consisted of a pool (180 cm diameter $\times$ 75 cm high) filled to a depth of 29 cm with water ($22 \pm 2^{\circ}$ C). The water was rendered opaque with white non-toxic tempera paint. A circular escape platform (14 cm diameter), submerged 1.0 cm below the surface of the water, was

located 38 cm away from the wall of the pool in the center of the northeast (NE) quadrant and remained there through all 4 days of testing. Two external cues were present, a black cabinet on south and an X sign on north. In addition the room had “natural” cues: a curtain on west and a sink on east. Each animal was given two trials a day. Each trial had a 60 sec ceiling, and the inter-trial interval ranged from 40 to 60 min. Vinpocetine or vehicle injections were given 4h before the first testing session. The animal was introduced into the pool, facing the wall of the quadrants northeast (NW), southeast (SE) or southwest (SW) (quadrants pseudo-randomly assigned). Once the animal reached the platform, it was allowed to remain on it for approximately 15 seconds. If the animal failed to reach the platform within 60 sec, the experimenter gently guided the animal through the water and placed it on the platform for 15 sec. Performance on each trial was recorded and analyzed with an image tracking software (Videomex-V, Columbus Instruments, Ohio). Latency to find platform, distance traveled, swimming speed and the percentage of time spent in each quadrant were calculated for each trial. Since there were highly significant correlations between latency and distance measures for all trials (Pearson correlation coefficients ranging from 0.84 to 0.99), we presented only the latency results in this study. The pool was divided in three concentric rings of equal area (inner, middle and outer) and the percentage of time spent in the outer ring was used to assess thigmotaxis and anxiety. The outer and mid ring had a width of 17 and 22 cm respectively. The inner (central) ring had a diameter of 51 cm. The platform was placed in the center of the mid ring.

Statistical analysis

All data were analyzed with repeated measures analyses of variance (rANOVA). The analyses of body weight during the ethanol or saline treatment (from PD4 to PD10) were carried out using “exposure” (ethanol or saline) as between-subjects factor and “day” as repeated within-subject factor. The rANOVAs for both body weight during the vinpocetine treatment and Morris maze data were carried out using “treatment” (CONT, ETOH or VINP) and “sex” (male or female) as between-subjects factors. Body weight data were analyzed with “day” as a repeated measure and “day” and “trial” served as repeated within-subject measures for the Morris maze data. Additionally, a univariate one-way ANOVA grouping the subjects by “treatment + quadrant” (CONT-NE, CONT-NW, CONT-SE, CONT-SW, ETOH-NE, ETOH-NW, ETOH-SE, ETOH-SW, VINP-NE, VINP-NW, VINP-SE, VINP-SW) was performed for percentage of time spent in each quadrant. Follow-up comparisons were conducted with least significant difference post hoc analyses.

Results

Blood ethanol concentration and survival rate

Blood alcohol levels (BAL, average $\pm$ SEM) one and three hours after injection (5g/Kg i.p.) were 239 ± 31 (n=4) and 216 ± 11.9 mg/dL (n=5), respectively. These levels are similar to our previous data in ferrets [22] and were higher than observed in mice [24]. The majority of the animals survived the saline and ethanol IP injections. Survival rates were 89.3% (n = 50) and 93.3% (n = 42) in ethanol and saline group, respectively. The difference between groups was slim and did not reach significance (Fisher’s Exact Test, $P = 0.73$). No animals died during treatment with vinpocetine or vehicle solution.

Offspring growth

Figure 1A shows offspring weights during the ethanol treatment. The body weights increased significantly from PD4 to PD10 [$F(1.4,30.8) = 709.9$, $P < 0.001$]. However, the saline-treated group presented a faster growth than the ethanol-treated group, as demonstrated by a significant Ethanol exposure X Age interaction [$F(1.4,30.8) = 35.8$, $P < 0.001$] as well as a main effect of Ethanol exposure [$F(1,22) = 17.4$, $P < 0.01$].

From PD25 to PD29, during the period of treatment with vinpocetine or vehicle solution, there was a significant increase in body weights [$F(1.3,51.1) = 1103.7$, $P < 0.001$]. The averaged body weight of the CONT group was higher than that observed for both the ETOH and the VINP groups [Treatment effect: $F(2,38) = 5.1$, $P < 0.01$], which did not differ from each other (Figure 1B). As indicated by a Treatment X Age interaction [$F(2.7, 51.1) = 3.0$, $P = 0.043$], the vinpocetine-treated subjects lagged in growth compared to the CONT group (FLSD, $P = 0.01$). The modest difference in gain weight observed in vinpocetine-treated animals may be an effect of phosphodiesterase inhibition on feeding. However, by chance, the alcohol-treated animals chosen to receive vinpocetine treatment were smaller than the ones that received vehicle (see fig 1B), which could explain this lag. Comparisons involving VINP and ETOH groups as well as CONT and ETOH did not reveal any differences in weight gain.

Morris water maze

While the latency to find the hidden platform decreases over time for all groups [Day effect: $F(2.4,90.8) = 11.2$, $P < 0.001$], Vinpocetine treatment significantly improved the performance of ethanol-treated rats in the Morris maze [Treatment effect: $F(2,38) = 4.9$, $P = 0.01$, Figure 2A and B]. The averaged latency of the ETOH group was significantly higher than that observed for both CONT and VINP groups, who did not differ from each other (Figure 2B). No significant differences were observed between males and females.

Figure 2C, illustrates that the swimming speed increased significantly from the first to the second day of testing [Day effect: $F(2.5,95.1) = 13.2$, $P < 0.001$] for all groups and stayed constant afterwards. No differences in swimming speed were observed between groups (Figure 2C and D), with no effect of treatment [$F(2,38) = 74.2$, $P < 0.48$] nor significant Treatment $\times$ Day interaction [$F(2,38) = 74.2$, $P < 0.48$]. This result indicates that the swimming performance was similar for all groups across the different testing sessions.

For all experimental groups, the percentage of time spent in the quadrant NE (with platform) did not change from the first to the second session but increased significantly from the second to the fourth session [Day effect: $F(1.5,58.2) = 5.4$, $P < 0.05$]. Interestingly, the univariate one-way ANOVA grouping the subjects by treatment + quadrant indicates that this increase was more accentuated in the CONT and VINP groups than that in the ETOH group [$F(11,175) = 1.97$, $P < 0.05$] (Figure 3). No significant differences were observed between males and females.

The percentage of time spent in the outer ring decreases from the first to the fourth session for all groups [Day effect: $F(2.6,97.1) = 37.3$, $P < 0.001$] (Figure 4A). As indicated by significant Treatment effect [$F(2,38) = 8.7$, $P < 0.001$], the CONT group had the smaller percentage of time in the outer ring than ETOH and VINP groups, who did not differ from each other (Figure 4B). No significant differences were observed between males and females.

Discussion

We showed that inhibition of PDE type 1 by vinpocetine improves learning performance in rats exposed to alcohol during the third trimester equivalent of human gestation. Importantly, vinpocetine treatment occurred long after the time of alcohol exposure, in a period that is equivalent to the adolescence in humans. Therefore, these findings may be relevant from a clinical standpoint since it opens the possibility for treating juveniles when prevention fails.

Early ethanol is known to affect stress response [25]. Our ethanol animals show a preference for periphery of the maze that might be attributed to a higher anxiety (Figure 4). Despite showing a better learning performance, alcohol-exposed animals treated with vinpocetine also

presented this behavior (Figure 4). Therefore, the beneficial effects of vinpocetine cannot be attributed to anxiolytic effects

There is growing evidence from several groups suggesting that impairment of neuronal plasticity in neocortex and hippocampus underlies some of the neurological deficits seen in FASD. For instance, *in vitro* electrophysiology studies showed that early alcohol exposure can disrupt Long Term Potentiation (LTP) [9] and *in vivo* electrophysiology studies showed that early alcohol exposure can impair neuronal plasticity in the barrel [26] and in the visual [22; 27] cortices.

The lingering effects of alcohol in learning performance may be linked to its effects on the cAMP response element (CRE) cascade [19;28;29]. Influx of calcium ions through the NMDAR channels activate protein kinases that, in turn, phosphorylate transcriptional regulators [30]. Of these regulatory elements, the CRE has remained in the spotlight as a mediator of synaptic plasticity and memory formation [30]. CRE function has been shown to be important for several experimental models of neuronal plasticity such as ODP [20], LTP and learning and memory [31]. Alcohol exposure during development can alter several key factors in the CRE cascade such as NMDA receptor function [32] and cAMP levels [33] and the expression of the plasticity related gene cFOS [34]. The expression of cFOS increases in the hippocampus of controls but not in alcohol-exposed animals after water maze testing [34]. This finding may be explained by recent findings showing that early exposure to alcohol results in a decrease in CREB phosphorylation in the hippocampus [29].

One of the current challenges in FASD research is to devise treatments that can be implemented long after the period of alcohol insult. In that regard, positive results have been demonstrated by improving AMPA receptor function with aniracetam [35] and by choline supplementation [11]. Here we provide evidence that Vinpocetine treatment may also reverse learning problems in FASD models, most likely due to activation of CREB cascade [17]. Vinpocetine treatment has been shown to facilitate LTP [15;36], enhance the structural dynamics of dendritial spines [37], improve memory retrieval [38], and enhance performance on cognitive tests in humans [18]. Recently, we showed that vinpocetine can also restore neuronal plasticity deficits caused by early alcohol exposure in the visual cortex of ferrets [19]. Therefore, together with the results presented here, Vinpocetine may be an important tool for the restoration of FASD related sensory problems.

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Figure 1.

Body weight gain (in grams) from Postnatal Day (PD) 4 to PD10 (A), and from PD 25 to PD 29 (B). Values represent means ($\pm$ SEM) from males and females combined. Note that ethanol exposure from PD4 to PD10 resulted in a significant body weight reduction, which persisted until P29. VINP = ethanol-exposed rats treated with vinpocetine; ETOH = ethanol-exposed rats treated with vehicle solution; CONT = saline-exposed rats treated with vehicle solution. *** $P < 0.001$ saline-exposed vs. ethanol-exposed; ** $P < 0.01$ CONT vs. VINP; # $P < 0.05$ CONT vs. ETOH.

Figure 2.

Mean ($\pm$ SEM) latencies to find the hidden platform (A and B) and swimming speeds (C and D) for all groups in the Morris water maze. In A and C, data represents averaged values by trial. In B and D, data represents averaged values from all trials in all testing days. Note that ethanol exposed animals took significantly more time to find the hidden platform than control animals and that vinpocetine treatment was able to restore the latency of ethanol-exposed animals to control levels. The swimming speed did not differ between groups. VINP = ethanol-exposed rats treated with vinpocetine; ETOH = ethanol-exposed rats treated with vehicle solution; CONT = saline-exposed rats treated with vehicle solution. ** $P < 0.01$, * $P < 0.05$.

Figure 3.

Mean ($\pm$ SEM) of percentage of time spent in each quadrant along sessions for the CONT (A), ETOH (B) and VINP (C) groups. In D, E and F are represented the respective mean differences between the second and the fourth sessions for each quadrant. The platform was positioned in the quadrant NE. Values were collapsed across trials over the training days. Note that the increase in time spent in the quadrant NE from the second to the fourth session was more pronounced in the CONT and VINP as compared to the ETOH group. VINP = ethanol-exposed rats treated with vinpocetine; ETOH = ethanol-exposed rats treated with vehicle solution; CONT = saline-exposed rats treated with vehicle solution. * $P < 0.05$, comparisons with NE quadrant.

Figure 4.

Mean ($\pm$ SEM) of percentage of time spent in the outer ring along sessions. Values were collapsed across trials over the training days. In A, values were collapsed across trials over the training days. In B, values were collapsed across both trials and day. Note that the CONT group spent less time in the center than that ETOH and VINP groups. VINP = ethanol-exposed rats treated with vinpocetine; ETOH = ethanol-exposed rats treated with vehicle solution; CONT = saline-exposed rats treated with vehicle solution. ** $P < 0.01$, * $P < 0.05$: CONT vs. ETOH; # $P < 0.01$, # $P < 0.05$: CONT vs. VINP.