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Neonatal serotonin (5-HT) depletion does not disrupt prepulse inhibition of the startle response in rats

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Abstract:
The neurodevelopmental hypothesis of many brain disorders is based on the notion that environmental factors have significant effects on brain maturation. Because serotonin (5-HT) dysfunction in development may be involved in disease etiology, the present investigation assessed the effects of neonatal 5-HT depletion on prepulse inhibition of the startle response (PPI) in rats. Three-day-old Sprague-Dawley rats were pretreated with desipramine (20 mg/kg), followed by an intraventricular injection of the selective 5-HT neurotoxin 5,7-dihydroxytryptamine (5,7-DHT, 70 μg dissolved in 2 μl of 0.1% saline solution in ascorbic acid) on each side. Three months later, the rats' PPI was tested. Despite a severe and permanent decrease (80–100%) in hippocampal, prefrontal and striatal 5-HT levels, treatment with 5,7-DHT caused no disruption of PPI. In contrast to this lack of effect, the 5,7-DHT treatment increased basal startle activity, as measured in response to a 120 dB stimulus. Thus, our results clearly indicate that neonatal 5-HT depletion does not interrupt prepulse inhibition in rats. Studies involving lesions of brain structures or chemical systems run the risk of inducing compensatory changes in brain function, resulting in an amelioration of any deficit. The development of such compensatory mechanisms seems likely in the current study, due to the severe and long-lasting effect of neonatal 5,7-DHT-induced reduction on 5-HT levels.

Key words:
prepulse inhibition, neonatal serotonin depletion, 5,7-DHT, rats

Abbreviations: 5-HIAA – 5-hydroxyindoleacetic acid, 5-HT – serotonin, 5,7-DHT – 5,7-dihydroxytryptamine, DA – dopamine, DHBA – dihydroxybenzylamine, DMI – desipramine hydrochloride, DOPAC – 3,4-dihydroxyphenylacetic acid, GABA – γ-aminobutyric acid, HPLC – high pressure liquid chromatography, HVD – homovanillic acid, MDMD – dihydroxyphenylacetic acid, 3,4-methylenedioxymethamphetamine, NA – noradrenaline, pCPA – *p*-chlorophenylalanine, PPI – prepulse inhibition of startle response

Introduction

The neurodevelopmental hypothesis of many brain disorders is based on the theory that environmental factors can have a significant impact on the processes required for brain maturation. Consequently, different

pharmacological (i.e., brain lesions) and non-pharmacological (i.e., isolation rearing and prenatal stress) models have been developed to study pharmacological manipulations of different transmitter systems [14, 21].

One of the most frequently used behavioral tests for assessing the inability to ignore irrelevant external stimuli is the prepulse inhibition paradigm (PPI). PPI refers to the decreased startle response to an intense stimulus (pulse) when this stimulus is immediately preceded by a weaker pre-stimulus (prepulse). Impaired sensorimotor gating, as reflected by altered PPI, has been reported to lead to thought disorders and cognitive dysfunctions [3, 6, 17, 37], such as schizophrenia [4, 25, 53], obsessive-compulsive disorder [47], Huntington's disease [49], nocturnal enuresis and attention deficit hyperactivity disorder [35], Tourette's syndrome [7], blepharospasm [16], non-epileptic seizure disorder [39] and post-traumatic stress disorder [18].

PPI is modulated by several brain systems. These systems include dopamine, glutamate, acetylcholine, γ-aminobutyric acid (GABA) and serotonin (5-HT) [14, 23]. A number of pharmacological agents that enhance 5-HT neurotransmission can disrupt PPI. These agents include the 5-HT releasers fenfluramine, *p*-chloroamphetamine, and 3,4-methylenedioxymethamphetamine (MDMD) [20]. Selective activation of 5-HT_{1A} [43, 44], 5-HT_{1B} [45, 46] and 5-HT_{2A} receptors [36,44] also has a disruptive effect on PPI. Interestingly, systemic or intracerebral administration of 5,7-dihydroxytryptamine (5,7-DHT) and *p*-chlorophenylalanine (pCPA) leads to a reduction in 5-HT levels, thereby resulting in disruption of PPI [12, 40]. This finding, together with those demonstrating similar effects following 5-HT agonist treatment, shows that 5-HT does not exert a bidirectional influence on sensorimotor gating; rather, it suggests that both increasing and decreasing 5-HT activity disrupts PPI.

Because 5-HT continues to have regulatory functions in the brain throughout adulthood, it is likely that early disruptions of 5-HT transmission would have important consequences for subsequent central nervous system development, organization and function. Several studies suggest that neurodevelopmental deficits induced by pre- or early postnatal events may also be significant risk factors for developing a disorder later in life [31, 41, 42]. Thus, it is possible that the loss of sensorimotor gating abilities may stem from developmental abnormalities in different neurotransmitter systems and associated brain structures.

The purpose of this study is to determine whether neonatal 5-HT lesions can produce deficits in prepulse inhibition in rats. The extent of the lesions was verified by quantification of monoamine levels using high-pressure liquid chromatography (HPLC).

Materials and Methods

Animals

Rats were housed in a temperature-controlled room (20–22°C) under a 12-h light/dark cycle (light on at 7:00 p.m.) and 60% relative humidity with access *ad libitum* to the granulated food (Labofeed H; WPiK, Kcynia, Poland) and tap water. All experiments were carried out between 8:00 a.m. and 4:00 p.m. The treatment of the rats was in accordance with the ethical standards of European and Polish regulations. All procedures were reviewed and approved by the local Ethics Committee on Animal Studies.

Timed pregnant Sprague-Dawley rats were obtained from a licensed breeder (Jagiellonian University Collegium Medicum, Kraków, Poland) and were singly housed in clear plastic cages containing wood chip bedding material. The age of newborn rats was determined by checking for births every day at 8:00 a.m. and 4:00.p.m. Three days after birth (the day of birth being postnatal day 0), the sex of the pups was determined, and males were submitted to further experimentation, as described below.

Drugs

The drugs 5,7-dihydroxytryptamine creatinine sulfate (5,7-DHT) and desipramine hydrochloride (DMI) were purchased from Sigma-Aldrich, (St. Louis, USA). To prevent oxidation, the 5,7-DHT neurotoxin was dissolved in 0.1% saline solution in ascorbic acid.

Neonatal lesion of 5-HT system with 5,7-dihydroxytryptamine

The detailed procedure was previously described by Jessa et al. [19]. Briefly, male pups (n = 38) were injected initially with DMI (20 mg/kg, *ip*), followed 60 min later by an intracisternal injection of 5,7-DHT. Neonates were individually removed from the litter

and, under ether anesthesia, were placed on a flat, brightly illuminated surface. The sterile needle, having a polyethylene sleeve up to 2 mm from the tip, was positioned 1.5 mm anterior to lambda and 2 mm lateral to the sagittal plane. After the needle was lowered into the two lateral ventricles, the 5,7-DHT solution was injected. The 5,7-DHT was administered at a dose of 70 µg of free base that was dissolved in 2 µl of 0.1% saline solution in ascorbic acid , in the volume of 2 µl on each side. Solvents were delivered with a flow rate of 1 µl/30 s. After completion of each infusion, the injector was left in place for 5 min to allow the neurotoxin to diffuse away from the site of injection. Control sham rats (n = 36) received the DMI injection and vehicle instead of 5,7-DHT. Dams were maintained with the litters until 28 days of age, when they were transferred (along with their foster littermates) to group cages. The 5,7-DHT-treated and control pups were weighed once a week. All experiments were carried out when animals reached 3 months of age.

Apparatus

Four startle chambers (SR LAB San Diego Instruments, San Diego, CA, USA) were used. Each startle chamber was enclosed in a 37.5 × 40.0 × 57.5 cm isolated cabinet and contained a transparent acrylic cylinder (inside diameter: 8.8 cm, inside length: 18.4 cm) located on a 12.5 × 25.5 cm Plexiglas platform. Acoustic noise bursts were presented *via* a loudspeaker mounted 24 cm above the cylinder. Movements within the cylinder were detected by a piezoelectric accelerometer attached to the base and transduced into signals that were rectified and recorded by computer. Sound levels in the chambers were measured and adequately calibrated with a sound meter. Response sensitivities were calibrated using the SR-LAB Startle Calibration System.

PPI testing

Test sessions began with placing the rat in the startle chamber with background white noise set at 69 dB. After a 5 min acclimation period, each subject was presented with 4 iterations of 16 types of trials (64 trials total): four background noise stimuli (69 dB for 40 ms), four prepulse stimuli (88 dB for 40 ms), four startle stimuli (120 dB for 40 ms) and four prepulse stimuli delivered 100 ms prior to a startle stimulus. Administration of trial types was randomized within each type of the four iterations, and the average intertrial interval was 25 s (range 20–30 s), across all 64 trials. Schematic representation of the PPI iteration is illustrated in Figure 1. The amount of PPI was expressed as the percentage decrease in startle response caused by presentation of the prepulse according to the following formula: PPI = 100 – [(mean startle amplitude on prepulse + pulse trials/mean startle amplitude on pulse alone trials) × 100]. Using this formula, a 0% value indicates no difference between the pulse alone and prepulse + pulse trials (i.e., no PPI). Increases in sensorimotor gating are reflected by higher percentage PPI values.

Neurochemistry

One day (24 h) after the final behavioral session, all rats were euthanized by decapitation, and their brains were quickly removed and dissected on an iced glass plate into three regions: the frontal cortex, the hippocampus and the striatum. Tissues were kept at –70°C until being used for experimentation.

Serotonin (5-HT), 5-hydroxyindoleacetic acid (5-HIAA), noradrenaline (NA), dopamine (DA), dihydroxyphenylacetic acid (DOPAC), and homovanillic acid (HVD) levels were assayed simultaneously using an HPLC system with electrochemical detection [24].

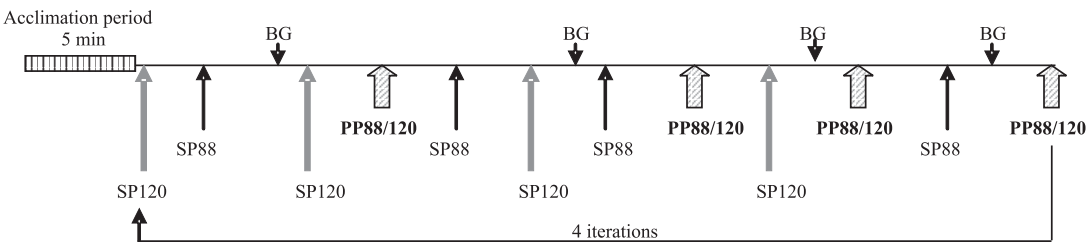

Fig. 1. Schematic representation of the PPI iteration. BG – background noise stimulus (69 dB for 40 ms), SP88 – prepulse stimulus (88 dB for 40 ms), SP120 – startle stimulus (120 dB for 40 ms), PP88/120 - prepulse stimulus (88 dB for 40 ms) delivered 100 ms prior to a startle stimulus (120 dB for 40 ms)

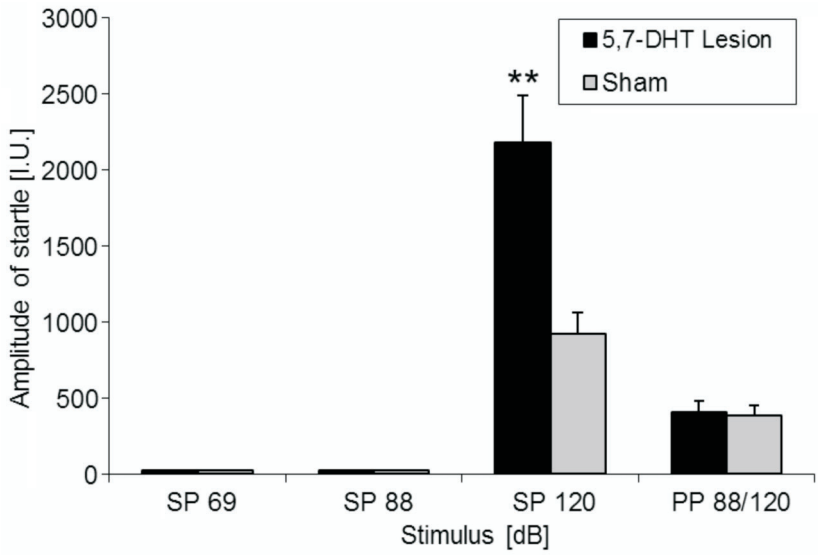

Fig. 2. Effects of neonatal 5-HT depletion on the mean startle amplitude to the 69 dB background noise stimulus (SP 69), 88 dB prepulse stimulus (SP 88), 120 dB startle stimulus (SP 120) and the 88 dB prepulse stimulus delivered 100 ms prior to the 120 dB startle stimulus (PP 88/120). Data represent the mean ± SEM of the startle amplitude averaged over 64 trials. ** $p < 0.01$ compared to the sham-operated control animals

Contents of monoamines were measured using liquid chromatography with an electrochemical detection HPLC system (Shimadzu, Japan) with a programmable flow rate and an LC-9A pump equipped with a 20 µl injection loop (Rheodyne, CA, USA). Separation of monoamines and their metabolites was carried out on a Nucleosil 7C-1B column (Macherey-Nagel, Germany) maintained at 32°C in a Shimadzu CTO-6A column oven. Integration of the chromatograms was performed with a Shimadzu C-R4AX Chromatopac-computing integrator. Dihydroxybenzylamine (DHBA) was used as an internal standard. The minimum level of detection of DHBA was 0.5 ng/ml; this concentration was injected onto the column. Levels of monoamines and their metabolites (ng/g of wet tissue) were subsequently calculated.

Statistical analysis

The statistical analysis was performed using the Statistica 7.0 software package (StatSoft, Inc., Tulsa, USA). The startle magnitude of each session was averaged and presented as the mean ± SEM. The lesions' effect on the baseline startle magnitude and PPI was evaluated using one-way ANOVA, followed by the *post-hoc* Newman-Keuls test. A probability value of $p < 0.05$ was considered to represent statistical significance. For neurochemical analysis, the one-way ANOVA was used. All *post-hoc* tests were performed using the Newman-Keuls procedure. All testing hypotheses used the probability value 0.05 as the level of significance.

Results

Effects of neonatal 5-HT depletion on startle baseline amplitude and PPI

The effects of neonatal 5-HT depletion on the startle baseline amplitude and PPI are shown in Figure 2. One-way ANOVA analysis revealed that neonatal 5-HT depletion caused no disruption of PPI [$F(1,72) = 0.10$, $p = 0.750$]. In contrast, the 5,7-DHT treatment led to an increase in basal startle activity, as measured in response to the 120 dB stimulus depletion [$F(1,72) = 12.30$, $p < 0.01$]. The mean level of sensorimotor gating was 83.27% for the 5,7-DHT-lesioned rats compared with 61.10% for the sham-operated rats.

Effects of neonatal 5-HT depletion on brain monoamine levels

In the frontal cortex (Tab. 1), neonatal 5-HT depletion was associated with significant reductions in 5-HT levels [$F(1,72) = 224.91$, $p < 0.01$], 5-HIAA levels [$F(1,72) = 209.77$, $p < 0.01$] and the ratio of 5-HIAA to 5-HT [$F(1,72) = 846.26$, $p < 0.01$]. No significant changes were observed in the NA, DOPAC, DA, HVA and HVA/DA levels.

In the hippocampus (Tab. 1), neonatal 5-HT depletion was associated with significant reductions in 5-HT levels [$F(1,72) = 53.85$, $p < 0.01$], 5-HIAA levels [$F(1,72) = 54.47$, $p < 0.01$] and the ratio of 5-HIAA to 5-HT [$F(1,72) = 17.25$, $p < 0.001$]. No sig-

Tab. 1. Tissue levels (ng/g of wet tissue weight) of monoamines and their metabolites in different brain regions of the 5,7-DHT-lesioned (n = 38) and sham-operated (n = 36) rats. Data are expressed as the mean ± SEM. ** p < 0.001 *vs.* sham-operated controls. ND = not determined

	Frontal cortex		Hippocampus		Striatum	
	5,7-DHT-lesioned rats	Sham-operated rats	5,7-DHT-lesioned rats	Sham-operated rats	5,7-DHT-lesioned rats	Sham-operated rats
5-HT	208.11 ± 22.43**	2358,9 ± 111.9	224.44 ± 27.22**	2422.9 ± 161.6	254.12 ± 54.12**	2567.7 ± 187.6
5-HIAA	143.22 ± 10.22 **	1023.4 ± 32.1	102.23 ± 18.22**	946.9 ± 67.2	130.21 ± 10.11**	1245.9 ± 39.1
NA	286.4 ± 27.2	270.4 ± 32.1	232.7 ± 19.6	245.3 ± 32.9	355.32 ± 26.1	342.8 ± 21.7
DA	1243,2 ± 144.9	1352,9 ± 141.4	ND	ND	11874.2 ± 511.34	12515.1 ± 678.4
DOPAC	191.4 ± 19.12	201.8 ± 18.2	ND	ND	7532.1 ± 156.3	7658.1 ± 134.2
HVA	6234.1 ± 289.1	6123.9 ± 223.4	4134.5 ± 411.4	4221.8 ± 388.1	9111.1 ± 311.2	8987.2 ± 334.1

nificant changes were observed in the NA, DOPAC, DA, HVA and HVA/DA levels.

In the striatum (Tab. 1), neonatal 5-HT depletion was associated with significant reductions in 5-HT levels [$F(1,72) = 208.85$, $p < 0.01$], 5-HIAA levels [$F(1,72) = 147.38$, $p < 0.01$] and the ratio of 5-HIAA/5-HT [$F(1,72) = 183.84$, $p < 0.01$]. No significant changes were observed in the NA, DOPAC, DA, HVA and HVA/DA levels.

Discussion

The most important discovery from this study was that neonatal 5-HT depletion caused no disruption of prepulse inhibition of the acoustic startle reflex in the adult rat. In contrast to the effect on PPI, treatment with 5,7-DHT increased basal startle activity, as measured in response to the 120 dB stimulus.

While the cortico-limbic-striatal-pallidal circuitry regulates the degree of inhibition by the prepulse, the startle response is controlled by the brain stem [11, 48]. The primary startle pathway includes several nuclei of the pontine reticular formation and connections with motoneurons of the spatial cord governing the muscle contraction [23]. Several factors, such as strain [50, 54], gender [2, 55], light cycle [13], or internal states, such as fear or anxiety [8], are known to affect the amplitude of the startle reflex in the rat. Furthermore, the fact that the startle amplitude is increased in states of fear (fear potentiation) and decreased in a pleasant context (pleasure attenuation) [22, 30] suggests that the startle reflex can be used to evaluate emotional states [23, 32]. Several studies have indicated that a reduction in brain 5-HT levels is associated with an increased sensitivity to various sensory stimuli [9, 10]. In our experiment, rats with neonatal 5-HT depletion had increased startle responses compared to sham-operated controls. These rats also revealed a decrease in social interaction and novel object exploration as well as an increase in anticipatory anxiety (unpublished data). Additionally, the total distance traveled and distance traveled in the central area of the open field test were significantly shorter in rats with neonatal depletion of 5-HT. This finding may suggest that fewer instances of novelty-seeking behavior and fear of new experiences may be responsible for the increased startle responses in rats with neonatal 5-HT depletion.

Our results are consistent with those of Walters et al. [52], who reported an increase in amplitude of the acoustic startle reflex in rats given a tryptophan-free diet. Only marked decreases in 5-HT levels (> 64%) were able to elevate the startle amplitude, suggesting that some critical level of 5-HT depletion must be reached to increase basal startle activity. Chronic treatment with the stimulant 3,4-methylenedioxymethamphetamine (MDMA) induced both a substantial 5-HT depletion and a strong increase in the baseline startle response in rats [33]. While rats with lesions in the median raphe nucleus tended to display higher startle responses compared to controls, there was no effect or trend toward an increase in rats with dorsal raphe nuclear lesions [15, 26, 27]. In contrast, injection of the neurotoxin 5,7-DHT into both the dorsal and median raphe nuclei did not alter basal startle

reactivity [12]. Unlike microinjections of the 5-HT_{1A} receptor agonist 8-OH-DPAT into the dorsal raphe nucleus [15], intraperitoneal administration of this selective agonist increased startle amplitude in rats [12]. No effect on startle responses was observed after intraperitoneal injections of the tryptophan hydroxylase inhibitor *p*-chlorophenylalanine (pCPA) [12, 40]. Finally, 5,7-DHT administration to the prefrontal cortex and nucleus accumbens septi produced an increase in baseline startle magnitude [34]. Taken together, these data suggest that depletion of 5-HT can augment the startle amplitude in rats. In our experiments, neonatal 5-HT depletion preferentially induced damage to the basic startle pathway over the prepulse inbition systems. Therefore, it appears that the effect of neonatal 5-HT depletion is probably on the basic startle reflex and not on the inhibitory pathways that modify startle reactivity; this possibility is supported by the PPI scores of neonatally 5,7-DHT-lesioned rats compared to those of the sham-lesioned rats (Fig. 2). Because 5-HT-depleted rats differ from their sham-operated controls on a measure of reactivity to the 120 dB startle stimulus alone, enhanced basal startle response may lead to an increase in sensorimotor gating (83.27% for the 5,7-DHT-lesioned rats *vs.* 61.10 % for the sham-operated rats). However, it appears that this neonatal 5,7-DHT-induced startle response is primarily an augmentation of the basic startle reflex rather than an effect on prepulse inhibition. A similar effect was reported in rats with 5,7-DHT injections into the nucleus accumbens [34].

In contrast to our results, recently published studies provide strong evidence that pharmacologically-induced depletion of 5-HT disrupts PPI. The 5-HT_{1A} agonist 8-OH-DPTA has been reported to disrupt PPI after local administration into the raphe nuclei, suggesting that it acts on 5-HT_{1A} somatodendritic receptors and causes a decrease in 5-HT neurotransmission [44]. Repeated treatment with the 5-HT synthesis inhibitor pCPA produced a small attenuation of PPI, but when combined with the 5-HT releaser (+)-fenfluramine, pCPA nearly abolished PPI [40]. Tryptophan depletion, which is known to decrease 5-HT levels in the central nervous system, attenuated PPI in humans without affecting basal startle reactivity [38]. Disrupted PPI was evident in animals treated either with the serotonin neurotoxin 5,7-DHT or with the tryptophan hydroxylase inhibitor pCPA [12]. Rats with median but not with dorsal raphe nuclear lesions showed marked and significant disruption of PPI [27], and this effect was reversed by acute treatment with clozapine and haloperidol [28]. Medial prefrontal cortex and basolateral amygdala injections of 5,7-DHT had no effects on PPI, but rats with 5,7-DHT-induced lesions of the central nucleus of the amygdala showed pronounced disruptions of PPI [28]. Prepulse inhibition was significantly altered in rats with lesions on the dorsal but not ventral hippocampus [29]. Finally, 5,7-DHT injections into the prefrontal cortex decreased PPI in rats [34]. In the present study, we observed a severe and permanent reduction in hippocampal, prefrontal and striatal 5-HT levels (Tab. 1); however, the depletion of 5-HT during neonatal development did not affect the processing of PPI of the acoustic startle reflex in the adult rat. While the reason for this inconsistency is unclear, some discrepancies may be attributable to animal-related factors, including the selection of the strain, sex, and age of rats being used, the impact of past startle experience, and the possible contribution of the developmental history of the animals prior to testing. Furthermore, when comparing findings across different laboratories, serious consideration must be given to basic methodological factors, such as the selectivity or potency of the drugs or manipulations for the serotonergic system, the test environment, stimulus parameters, procedures, experimental designs, equipment, and measures used to quantitate both startle response and PPI.

The predictive validity of the 5-HT model of PPI disruption appears to be weakened by results from human subjects [4]. Specifically, the 5-HT releaser MDMA increases PPI in humans, rather than disrupting PPI, as observed in rats [51]. Nevertheless, because the effects of MDMA on PPI in humans appear to be the opposite of those seen in rats, the predictive validity of the 5-HT model of PPI disruption is compromised at present.

In conclusion, our results clearly indicate that neonatal 5-HT depletion does not interrupt prepulse inhibition in rats. Studies involving lesions of brain structures or chemical systems run the risk that inducing compensatory changes in brain function can lead to amelioration of any deficit. Such compensatory changes have previously been reported following 5,7-DHT-induced damage to 5-HT neurons [1]. The development of such compensatory mechanisms seems possible in our experiment because the ability of neonatal 5,7-DHT-induced reductions in 5-HT levels to reduce PPI was severe and long-lasting.

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