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Long Latency Event-Related Potentials in Rats: Effects of Dopaminergic and Serotonergic Depletions[1]

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EHLERS, C. L., T. L. WALL AND R. I. CHAPLIN. *Long latency event-related potentials in rats: Effects of dopaminergic and serotonergic depletions*. PHARMACOL BIOCHEM BEHAV **38**(4) 789–793, 1991.—The effects of serotonergic and dopaminergic depletions on event-related potentials (ERPs) generated by an auditory "oddball" paradigm were evaluated. Eighteen rats received either sham or six-hydroxydopamine (6-OHDA) lesions to the ventral tegmental area (VTA), and were subsequently implanted with electrodes in the frontal cortex, dorsal hippocampus (DHPC), and amygdala (AMYG). In these animals, a series of large amplitude potentials in the 10–200 ms latency range could be recorded from all the brain areas tested. In addition, late positivities (in the 300–400 ms range) were identified in DHPC and AMYG. 6-OHDA lesions to the VTA were found to produce a 30–46% reduction in dopamine, but did not significantly alter any of the ERP components. A second series of rats were implanted with electrodes in cortex and DHPC. These rats then received vehicle injections and subsequently injections of parachlorophenylalanine (PCPA). PCPA produced a 50% depletion of serotonin concomitant with significant reductions in the negative components in the 50–100 ms range recorded in hippocampus and cortex. These studies support a role for serotonin but not dopamine in the processing of passively presented auditory stimuli and further suggest that the rat may be a good model for the exploration of long latency ERPs.

Long latency event-related potentials Dopamine Serotonin

THE study of long latency event-related potentials (ERPs) in humans has provided data helpful in forging a link between scalp-recorded electrophysiological events and such cognitive processes as selective attention, classification of stimuli, and memory [see (11)]. Over the last several years animal models of these ERPs have also been developed in an attempt to isolate the physiological processes underlying these electrophysiological events. Most animal studies have focused on recording the P3 or P300 component of the ERP usually using a modification of an auditory "oddball" paradigm. Using these paradigms, P300 waves which resemble those recorded from human subjects have been recorded from unanesthetized monkeys (1, 3, 4, 7, 18, 20–22), cats (2, 9, 10, 28) and rats (5, 6, 12, 19).

Some of these studies have also utilized lesion techniques to evaluate the possible generators of these "P300-like potentials" in animal subjects. A series of studies (9,10) has found that while primary auditory cortex ablation does not abolish the P3 recorded from cat skull, septal lesions can produce profound reductions in the cat P3 amplitude. In another recent study, Pineda et al. (22) made electrolytic lesions and knife cuts to the area of the locus coeruleus and found that monkey P300-like potentials, also recorded from skull, exhibited decreased areas, altered brain-surface distribution, and reduced sensitivity to stimulus probability. Taken together, these studies support the concept that certain subcortical systems may be important for the generation of these "P300-like" potentials recorded in animals.

We have recently reported that long latency ERPs can be recorded from unanesthetized rats presented a passive auditory "oddball" paradigm (5,6). Such passive paradigms, where subjects are not instructed to respond to the stimuli, have been used in humans to generate a positive going potential which has a fronto-central distribution and has been labeled the P3a (25). Depth recordings from the regions of frontal cortex and dorsal hippocampus revealed that several ERP components could be obtained from Wistar rats presented this paradigm with latencies in the 10–200 ms range which differed in their polarities, amplitudes, and morphology depending on the recording site. In this study, late positivities in the 250–400 ms range were also recorded but only from electrodes which were aimed at the dorsal hippocampus (5,6). Thus these studies are supportive of the hypothesis that limbic sites such as the hippocampus may participate in the generation of the late positivities in the 300 ms latency range recorded following the presentation of passive stimuli.

The present study was undertaken to extend our previous rat studies to evaluate whether these late positivities could also be

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identified in another limbic site, the amygdala, and to test whether dopaminergic and serotonergic depletions could modify ERP morphology.

METHOD

Subjects

The experimental subjects were male Wistar rats weighing between 280–300 grams, who were housed in controlled temperature and lighting conditions. Each animal was handled for five minutes three times over a seven-day period prior to the surgical procedures. In order to lesion the mesolimbic dopaminergic neurons, nineteen rats were randomly assigned to either a sham or lesion group. Under pentobarbital anesthesia (Nembutal, 50 mg/kg IP) nine rats received bilateral six-hydroxydopamine (6-OHDA) lesions to the region of the ventral tegmental area (VTA). Bilateral cannulae were lowered to: toothbar +5.0, AP +2.8, L 0.5, V −8.7 (from earbar zero). The 6-OHDA (4 mg/ml) was dissolved in a 0.1 mg/ml ascorbic acid solution and 1 μl was infused to the left and right VTA over a six-minute period using a Hamilton microliter syringe attached to a Harvard infusion pump. Ten sham-lesioned animals received equal volume injections of the ascorbate/saline vehicle. Following placement of the lesions or sham treatments, all rats were immediately implanted with stainless steel single wire electrodes using bregma reference in the dorsal hippocampus (toothbar +5.0, AP −3.0, ML 3.0, PV −3.0), amygdala (toothbar +5.0, AP +1.0, ML 6.0, DV −9.5) as well as stainless steel screws placed in the calvarium over frontal cortex and 3 mm posterior to lambda. Hippocampal placement was verified by the presence of characteristic theta activity, coordinates for amygdala, and VTA were based on previous lesion data (14).

A second series of eight rats were surgically prepared prior to depletion of serotonin via PCTA treatment. Under pentobarbital anesthesia, stainless steel unipolar electrodes were stereotaxically placed in all eight rats in the hippocampus (coordinates as above), and screw electrodes were placed in the calvaria over the frontal cortex. A ground electrode was also placed in the calvarium 3 mm posterior to lambda. Electrode connections in all rats were made through an amphenol connector and the entire assembly attached to the calvaria with dental acrylic. All rats were allowed at least three weeks to recover prior to any experimental procedures.

Recording Procedures

For ERP recordings animals were placed in a Naugahyde sling which comfortably supported the animal in an awake state, but prevented movement-induced artifact. The sling was placed in an electrically shielded light-, sound- and temperature-controlled BRS/LVE recording chamber. All animals were adapted to the chamber prior to the recording sessions. On a test day, rats were singly placed in the chamber and a connector attached to a microdot cable was used to transfer the monopolar (referred to lambda) EEG signals to a polygraph. Animals were grounded via the lambda screw. The bandpass for recording was set at 0.3–70 Hz with a 60 Hz notch filter in. The EEG, as well as calibration signals, were transferred from the polygraph on-line to a DEC (LSI 11-2) computer which also controlled the presentation of the auditory stimuli. Free field auditory stimuli were presented through a small speaker centered approximately 20 cm above the rat's head. ERPs were elicited with an acoustic "oddball" paradigm. The tones were generated by a programmable multiple-tone generator, the characteristics of which have been described previously (24). The acoustic parameters for this paradigm were two square wave tones (rise/fall time <1 ms) a frequent or "standard" tone (20 ms, 1 kHz, 70 dB SPL) presented 84% of the time and an infrequent or "rare" tone (20 ms, 2 kHz, 85 dB SPL) presented 16% of the time. Rare tones were interspersed with standards such that no two rare tones occurred successively. The digitizing epoch for each trial was one second and a 0.5–1 second intertrial interval was used. The total number of trials in a recording session was 150. Animals were only tested once per test day and at least seven days lapsed between testing.

Experimental Testing

All rats were allowed at least three weeks to recover from the surgical procedure. ERPs were obtained from rats with sham and 6-OHDA lesions to the VTA, at four weeks postsurgery. In the second series, rats were given three daily SC saline injections and ERPs were recorded twenty-four hours following the third saline treatment. The following week these same rats were given three daily SC injections of 150 mg/kg PCPA and ERPs were again measured twenty-four hours following the third injection. Following the termination of the experimental procedures, rats were decapitated and the brains removed and quickly frozen. The brains were subsequently microdissected, and assayed for catecholamine content using a modification of the methods of Kilts and Anderson (15).

Data Analysis

The ERP trials were digitized at a rate of 256 Hz. Trials containing excessive movement artifact were eliminated prior to averaging (<5% of the trials). An artifact rejection program was utilized to eliminate individual trials in which the EEG exceeded +250 μV. The ERP components were qualified by computer by identifying a peak amplitude (baseline-to-peak) within a standard latency range. The baseline was determined by averaging the 100 ms of prestimulus activity obtained for each trial. Components were labeled based on their polarities and their relative latencies. For instance, the first positive peak was labeled the P1 (first positive going potential), the next identifiable wave was designated the N1, etc. The latency of a component was defined as the time of occurrence of the peak amplitude within a latency window. The latency windows for cortex were: P1, 0–50 ms, N1a, 25–80 ms; and N1b, 50–100 ms. The windows for dorsal hippocampus were: P1, 0–50 ms; N1, 25–80 ms; P2, 150–250 ms; and P3, 250–350 ms. The latency windows for amygdala were P1, 10–50 ms; N1a, 50–75 ms; P2, 150–250 ms; and P3, 250–400 ms.

Analysis of variance (ANOVA) was utilized to statistically evaluate the data. In order to compare differences between the ERPs recorded following the presentation of tone 1 and tone 2, and saline vs. PCPA treatment at each electrode site, a within subject's design was utilized. A between subjects ANOVA was used to determine if differences in ERP amplitudes and latencies existed between sham and lesioned rats.

RESULTS

The presentation of infrequent (rare, loud) auditory tones embedded in a sequence of frequent (standard, soft) tones to Wistar rats was found to produce a series of waves which could be averaged from the EEG. Figure 1 presents the response of anterior cortex, dorsal hippocampus, and amygdala to the passive auditory "oddball" paradigm in the sham-lesioned animals. The response of auditory cortex to the frequent, soft tone consisted of any early positive component (P1) with a latency of 25 ms followed by a broad negative designated the N1 wave (first negative

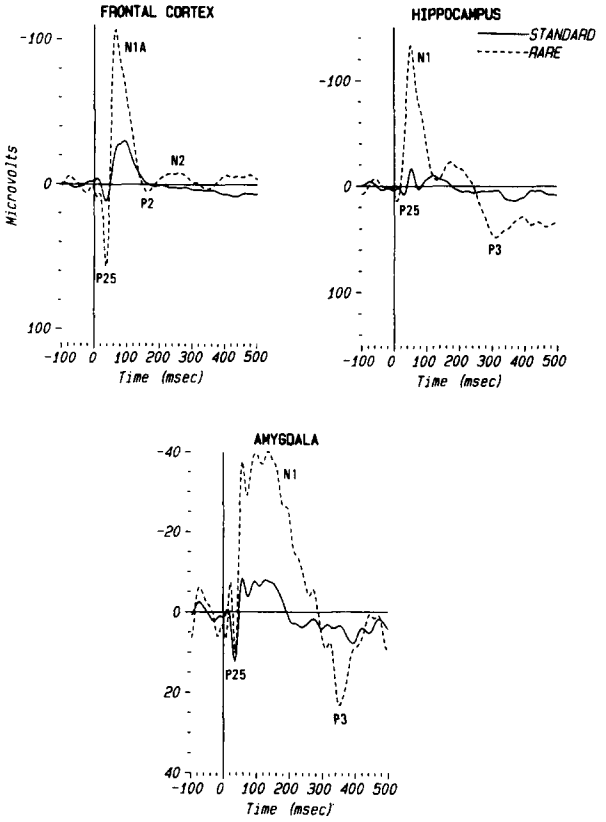

FIG. 1. Event-related potential "Grand Averages" from 10 sham-lesioned rats for frontal cortex, dorsal hippocampus and amygdala. Potentials are recorded concurrently from all electrode sites in each animal. Approximate locations of the ERP components (e.g., N1, P1, N1a, N1b, P1a, P1b, N2, P2, and P3) observed following the rare (loud) and standard (soft) tones are illustrated. A late positive potential in the 250–400 ms latency range was recorded from amygdala and hippocampal electrodes.

peak) which had a peak latency of 60–80 ms. The amplitude of the P1, $F(1,10)=5.47$, $p<0.04$, and the N1 response, $F(1,10)=41.88$, $p<0.001$, were found to be significantly higher following the infrequent, loud tone, compared to the standard. The N1 response to the infrequent tone could also be more clearly differentiated into two separate waves, the N1A with a latency of 50–70 ms and an N1B with a latency of 80–100 ms.

The response of the dorsal hippocampus (DHPC) to the standard (soft) tone consisted of an early positive potential (P1), which occurred at about 25 ms, followed by a high amplitude negative wave (N1) with a latency of about 40–60 ms, and a later positive wave (P2), with a latency of 100–200 ms. Hippocampal ERPs from the rare (loud) tone differed from the standard (soft) tone in that the amplitude of the P1 following the rare tone was significantly higher, $F(1,9)=21.08$, $p<0.001$, and the N1 amplitude was doubled, $F(1,10)=15.36$, $p<0.003$. In addition, a third positive wave (P3) which occurred at a latency of 250–350 ms could clearly be identified following the rare tone which significantly differed in amplitude from the peak signal amplitude in that latency range seen following presentation of the standard tone, $F(1,10)=14.452$, $p<0.003$.

The response of the amygdala (AMYG) to the standard (soft) tone consisted of an early positive potential (P1) followed by a complex group of negative waves with a latency of 50–150 ms and a later positive complex of waves (P2–P3). ERPs from the rare (loud) tone differed from the standard in that the amplitude of the N1a, $F(1,10)=19.7$, $p<0.001$, and N1b, $F(1,7)=22.94$, $p<0.002$, waves were significantly increased. A third positive wave (P3) which occurred at a latency of 250–400 ms could also be identified following the rare tone, $F(1,10)=8.15$, $p<0.02$, as opposed to the standard.

Neurochemical analysis of the sham and 6-OHDA-lesioned rats at 18 weeks postsurgery revealed that partial, but significant, $F(1,10)=6.49$, $p<0.03$, depletion of dopamine was caused by the lesions. A mean reduction of 32% was observed in the nucleus accumbens (mean ± SEM) (shams, 11.25 ± 2.62; lesions, 7.94 ± 1.28 ng/mg PROT), 46% in the amygdala (shams, 10.15 ± 1.19; lesions, 5.58 ± 0.92 ng/mg PROT) a 30% reduction in the frontal cortex (shams, 1.66 ± 0.3; lesions, 1.29 ± 0.52) and a 47% reduction in cingulate cortex (shams, 4.58 ± 1.11, lesions, 2.74 ± 0.94). However, no significant differences were noted between sham- and 6-OHDA-lesioned rats in any of the ERP components from any of the electrode sites (data not shown).

Significant reductions in the levels of serotonin were also found when levels in PCPA-treated rats were compared to values observed in sham-treated rats utilized in previous studies, $F(1,15)=18.20$, $p<0.001$. A 55% reduction in 5-HT was observed in frontal cortex (means ± SEM) (shams, 4.47 ± 0.4; PCPA-treated 2.04 ± 0.4) and a 50% reduction in hippocampus (shams, 4.24 ± 0.6; PCPA-treated 2.14 ± 0.4 ng/mg PROT). Significant differences in ERP components were also observed when responses following saline injections were compared to those seen after PCPA treatment. As seen in Fig. 2, PCPA injections primarily produced reductions in the amplitude and increases in the latency of the N1 in the cortical leads. A significant reduction in the amplitude of the N1 response to the standard, $F(1,8)=26.8$, $p<0.001$, and rare, $F(1,8)=27.2$, $p<0.001$, tones was observed as well as an increase in the latency, $F(1,8)=8.84$, $p<0.02$, of the N1 response to the standard tone. A reduction in the amplitude of the hippocampal N1 response to the standard tone was also seen in the PCPA-treated rats, $F(1,8)=7.98$, $p<0.02$. No changes in the amplitude or latency of later waves, in the 150–400 latency ranges, were noted as a result of PCPA treatment.

DISCUSSION

These studies demonstrate that long latency ERP components can be recorded from rats following presentation of a passively presented auditory "oddball" paradigm. These ERPs differed in their latencies, amplitudes, and morphology depending on the recording site. ERPs obtained from skull screws placed over the frontal cortex contained an early positive wave (P1) as well as a two peaked negative wave, designated the N1a and N1b. No late positivities were noted in ERPs recorded in cortex. These findings of tone sensitive negativities in the 50–100 ms range in cortex provide confirmation of earlier studies when identical stimulus responsive ERPs were obtained from cortex in unanesthetized rats (5). No late positivities in the 300–400 ms range were observed in the cortical areas. These findings are also consistent with studies in monkeys where P300s were also not detected in frontal leads (1).

ERPs recorded from the regions of the hippocampus and amygdala were found to have a different morphology than those obtained from cortex. In hippocampus, an early negative wave, designated the N1, could be detected following the standard and rare tones. This wave occurred at about 50 ms latency, whereas the N1 in cortex occurred at about 70 ms in latency. In amygdala, a series of negative potentials (N1's) were recorded, the first of

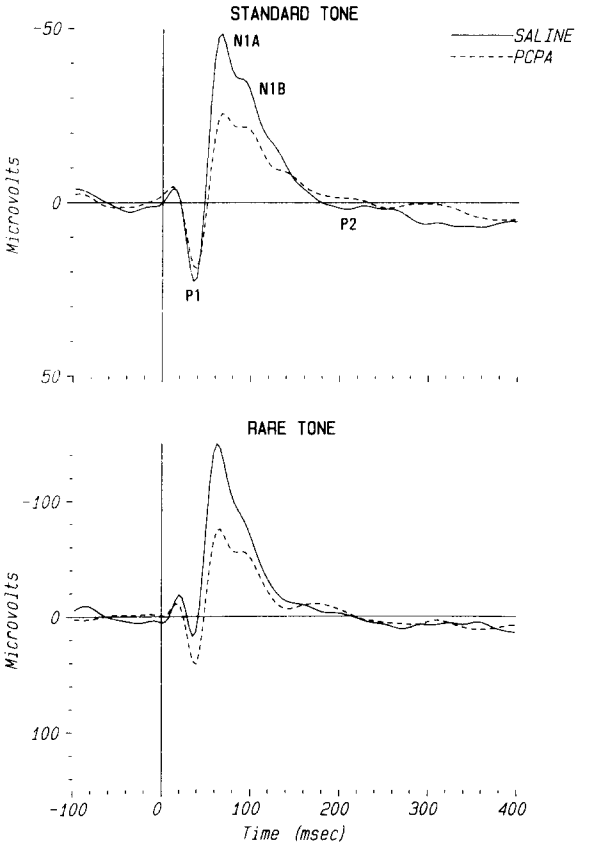

FIG. 2. Event-related potential "Grand Averages" from 8 rats recorded from cortical leads following saline and PCPA injections. Approximate locations of the ERP components (e.g., P1, N1a, N1b, and P2) are illustrated. PCPA was found to significantly reduce the amplitude of the negative component recorded in cortex and DHPC in the 50–100 ms latency range following the standard (soft) and rare (loud) tones.

which also occurred at about 50 ms. Two additional positive waves designated the P2 (100–200 ms) and the P3 (250–350 ms) were observed following the rare tone in DHPC. These late positive potentials recorded in DHPC were also observed in our previous studies (5,6). A late positivity was also found to occur following presentation of the rare tone in the region of the amygdala, a brain area not previously recorded from. The late positivity recorded from amygdala had a slightly different morphology from those recorded in hippocampus and also appeared to occur after a somewhat longer latency. These findings of a late positivities in hippocampus and amygdala of the rat are supportive of studies in human subjects where intercranial P3 potentials have been recorded in hippocampus and amygdala (8, 18, 30). However, there is also good evidence to suggest that cortical sites may contribute to the generation of the P3 in human subjects (15). Studies in cats also lend support to the idea that the hippocampus may be an important generator of the cat P3 as lesions to the septum, an important input to the hippocampus, were found to cause P3 waves recorded over cortex to disappear (10). In contrast, lesions of the cat auditory cortex were not found to modify P3 morphology in cats (9).

Our findings, however, are not entirely consistent with other investigators which have utilized rats (12,19). In one study a wave labeled as a "P300" was recorded from unanesthetized rats (12); in another study, anesthetized rats were used (19). In both studies, only cortical sites were recorded from the electrode locations appeared to be near or posterior to bregma. Since this area of cortex somewhat overlays the hippocampal formation, it is possible that volume conduction may have contributed to the waveforms recorded in those studies. Further studies using current source density analysis might be helpful to order to resolve this issue of wave location and latency in several brain areas.

Rat ERP components have also been found to be sensitive to changes in brain amine levels. In a previous study, we found that 6-OHDA lesions to the area of the dorsal noradrenergic bundle produced a 50% reduction in hippocampal norepinephrine (NE) as well as a significant reduction in the amplitude of the hippocampally recorded late positivity in the rat (unpublished observations). Those findings are also consistent with data reported by Pineda et al. (22) in squirrel monkeys where destruction of noradrenergic neurons of the locus coeruleus were found to modify monkey "P300-like" potentials recorded at the cortical surface.

In the present study, 6-OHDA lesions to the dopamine-containing cell bodies of the ventral tegmental area were found to produce a significant (30–47%) reduction in dopamine (DA) in the target areas (frontal cortex, nucleus accumbens, amygdala). However, no modification of ERP components were found. These data suggest that the loss of noradrenergic input to the forebrain can modify ERP components, but that dopaminergic input may not be an important regulator of ERP amplitudes or latencies. However, it is possible that the reductions in the DA observed in the present study were not substantial enough to produce electrophysiological changes at the target sites. Behavioral studies in rats have suggested that dopamine may regulate certain aspects of locomotion as well as "motivated" or "rewarding" behaviors (13, 26, 29). In the present study, rats were presented tones under "passive" behavioral conditions. Thus dopamine may not regulate ERP potentials recorded under passive conditions, but might be expected to alter potentials recorded under "active" or "motivated" task situations.

PCPA injections were found to modify rat ERPs by producing a reduction in the negative going potentials in the 50–100 ms range recorded in cortex and hippocampus. The fact that N1 components were found to be reduced in both hippocampus and cortex (AMYG was not recorded from these animals) following PCPA treatment, lends further support to the concept that the N1 recorded at these two sites may be modified by similar inputs. In human studies, the N1 is considered an exogenous component and has been associated with arousal and attention as well as physical aspects of the stimuli (11). However, it is not clear whether the negativities recorded in rats are functionally equivalent to the waves recorded in humans in the same latency ranges. In animal studies, PCPA has been reported to retard the acquisition of passive avoidance learning in rats (27). It is possible that such deficits in learning may be related to reductions in the negative potentials observed in the present study.

Taken together, our studies suggest that a series of long latency ERPs can be reliably recorded from rodents presented a passive auditory "oddball" paradigm. Specifically, it was found that late positivities in the 250–400 ms latency range could be recorded in rat limbic sites such as amygdala and hippocampus. PCPA treatment was observed to produce reductions in negative components recorded in the 50–100 ms range, in cortex and DHPC. 6-OHDA lesions to the VTA were found to be ineffective in modifying any ERP components. Finally, these findings point toward the rat as a potentially new model in which to explore the psychophysiological basis of long latency ERPs.

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