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Chronic corticosterone treatment alters sensory gating in C3H mice

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Abstract

Two methods of evaluating inhibitory sensory processing are prepulse inhibition of acoustic startle (PPI) and gating of auditory evoked potentials. Studies using both methods suggest nicotinic acetylcholinergic receptor modulation of gating, specifically the α-bungarotoxin (α-BTX) binding site (α7 receptor subtype). However, recent assessment of α7 null mutant mice failed to demonstrate any effect of the loss of this receptor in either gating paradigm. An alternate approach to assessing the effects of the α7 receptor is to reduce its numbers in mature inbred mice, thus, avoiding the twin problems of background and developmental compensation inherent in null mutant mouse studies. Numerous studies have shown that chronic corticosterone (CCS) treatment selectively reduces α-BTX binding sites. C3H mice were adrenalectomized and implanted with corticosterone or cholesterol (control) pellets. After 8 days, they were tested in one of the gating paradigms. PPI and auditory gating were significantly diminished in corticosterone-treated mice concomitant with a reduction in α-BTX binding in several brain regions. Cholesterol-treated mice had no change in either paradigm. Nicotine treatment (1 mg/kg) produced significant improvement in both paradigms in corticosterone-treated mice. These data agree with previous pharmacological studies suggesting modulation of gating occurs through a nicotinic receptor.

Keywords: Prepulse inhibition; Acoustic startle; Sensorimotor gating; Sensory gating; Sensory inhibition; Auditory gating; Schizophrenia; Nicotine; Nicotinic receptors; α-Bungarotoxin; Corticosterone; Mice

1. Introduction

Prepulse inhibition of acoustic startle (PPI) and gating of auditory evoked potentials have classically been used to assess inhibitory sensory processing functions. PPI is characterized by a decrease in the amplitude of the acoustic startle response when the startling stimulus is preceded by a small, nonstartling auditory stimulus, whereas in auditory gating there is a decrease in the electrophysiological response to the second of closely paired identical auditory stimuli. Both PPI and auditory gating paradigms lend themselves to testing in rodents. Early studies using 19 inbred mouse strains demonstrated a strain-dependent variation in acoustic startle (Marks et al., 1986). A subsequent study showed strain-dependent variation in PPI (Bullock et al., 1997). The latter study, which used six inbred mouse strains that varied maximally in acoustic startle, also detected a significant correlation between the levels of α-bungarotoxin (α-BTX) binding in the hippocampus and the degree of PPI (high binding strains showed the greatest startle inhibition). In the auditory gating paradigm, studies across nine inbred strains of mice also demonstrated a significant correlation between the levels of hippocampal α-BTX binding, specifically in the CA3 region, and the capacity for exhibiting auditory gating (Stevens et al., 1996). α-BTX binds to α7-containing nicotinic receptors (Barrantes et al., 1995). The best evidence for this assertion is α-BTX binding is totally absent in α7 null mutant mice (Orr-Urtreger et al., 1997). The finding that the degree of PPI and auditory gating covary with differences in levels of hippocampal α-BTX binding suggest that this binding site plays a key role in regulating sensory inhibition. A potential problem with this interpretation is a gene or genes tightly linked to the α7 nicotinic receptor may be responsible for the covariance between behavior and biochemistry.

Recently, Paylor et al. (1998) reported that acoustic startle and PPI are normal in α7 null mutant mice, a finding

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we have replicated (unpublished). Similarly, preliminary studies from our laboratory (unpublished) suggest that auditory gating is also normal in the α7 null mutant mice. These results shed doubt on the hypothesis that the α-BTX binding site plays a role in regulating these behaviors. However, data obtained with null mutants must be interpreted cautiously. Recent evidence suggests that compensatory processes may be triggered as a consequence of gene deletion, at least for some genes (Dumartin et al., 2000; Fauchey et al., 2000). This is a concern with the α7 null mutants because no effect of gene deletion, other than a loss of α-BTX binding and α7 mRNA, has been identified, to date (Orr-Urtreger et al., 1997; Paylor et al., 1998). Homozygous null mutant mice demonstrate normal neurological function, normal general appearance, growth, survival and anatomy. This contrasts with results obtained with mice that are homozygous for the L250T mutation of the α7 gene (Orr-Urtreger et al., 2000). Genetically engineered mice that are homozygous for this mutation die shortly after birth and show extensive apoptotic cell death throughout the somatosensory cortex, thereby demonstrating that alterations in functional properties of the α7 gene product (the L250T mutation results in a decreased rate of desensitization (Bertrand et al., 1992; Revah et al., 1991) result in altered brain development and, presumably, function. Another factor that may influence the effects of gene deletion is genetic background; effects of gene deletion may not be seen on some genetic backgrounds. For example, recent studies from our group (Bowers et al., 1999, 2000) have shown that deletion of the PKCγ gene results in altered behavioral responses to ethanol when the null mutation is expressed on a mixed 129-C57BL/6 background, whereas no effect of the null mutation was seen when the background was nearly 100% C57BL/6. There is no guarantee that genetic background influences the effect of gene deletion for α7. Nonetheless, the finding that PPI and auditory gating appear normal in these mice must not be taken as proof that the α7 gene product does not influence these behaviors.

An alternate approach to determining if the nicotinic α7 receptor is involved in regulation of inhibitory sensory processing would be to alter the numbers of these receptors in adult mice from a pure inbred mouse strain. This would avoid the twin problems of background and developmental compensation inherent in null mutant mouse studies. Several studies from our laboratory have demonstrated that chronic corticosterone (CCS) treatment results in a reversible decrease in brain α-BTX binding (Grun et al., 1995; Pauly and Collins, 1993; Pauly et al., 1988, 1990; Robinson et al., 1996; Stitzel et al., 1996). CCS treatment, via subcutaneously implanted corticosterone pellets, reliably increased plasma corticosterone levels and produced regional reductions in α-BTX binding. The decrease varies with brain region, however, the hippocampus appears to be uniquely sensitive to this effect. The experiments described here used this method to alter the number of α-BTX binding sites (α7 nicotinic receptors) in C3H mice, an inbred mouse strain with high hippocampal α-BTX binding (Marks et al., 1989), high PPI (Bullock et al., 1997) and normal auditory gating (Stevens et al., 1996). These mice are also the most sensitive of five strains that have been studied (C3H, C57BL/6, DBA/2, LS, SS) to adrenalectomy (ADX)-induced increases in α-BTX binding (Pauly et al., 1990) and CCS-induced decreases in binding (Stitzel et al., 1996). This strain is also most sensitive to nicotine-induced increases in acoustic startle (Orr-Urtreger et al., 2000).

Poor inhibitory processing is thought to underlie the sensory flooding and personality decompensation associated with schizophrenia (Venables, 1964, 1992). Both the PPI and auditory gating paradigms have been used to assess sensory inhibition in both schizophrenia patients and control individuals (Adler et al., 1982; Baker et al., 1987; Braff et al., 1992, 1995; Freedman et al., 1987; Parwani et al., 2000) as well as in animal models (Bertrand et al., 1992; Paylor et al., 1998; Stevens et al., 1991). As noted above, α7 nicotinic receptors have been implicated in the regulation of gating in both gating paradigms, and CCS has been shown to reduce the numbers of these receptors in selected brain regions. However, it is not known if reduction of α7 receptors through this method can be linked to impairment of sensory gating in the same animals. The present studies address this question.

2. Methods

2.1. Animals

Male C3H/2/ibg mice were bred at the Institute for Behavioral Genetics, University of Colorado, Boulder, CO. This strain has been maintained at the Institute for at least 20 generations. All mice were housed with male littermates. Animals were 60–90 days of age when tested. A 12-h light/dark cycle was maintained and animals were given free access to food (Teklad Rodent Chow) and water. All procedures performed on the animals were approved by the Institutional Review Committee for the use of Animal Subjects at the University of Colorado, Boulder, CO, or at the University of Colorado Health Sciences, Denver, CO, and conform to the NIH Guide for the care and use of laboratory animals.

2.2. Preparation of hormone pellets

The steroid pellets were made as described in Pauly et al. (1990) and contained 60% corticosterone (Sigma, St. Louis, MO) and 40% cholesterol (Sigma) by weight. Control pellets contained only cholesterol. Molten hormone mixtures were pipetted into the reservoirs of a one-grain pharmaceutical pellet mold. A small amount of peanut oil was added to the hormone mixture to make the pellet less brittle; the pellet mold was lubricated with polyethylene glycol (Sigma) to make the pellets easier to remove.

2.3. Surgery

Mice were anesthetized by intraperitoneal injection of pentobarbital (54 mg/kg). A small incision (approximately 1 cm) was made in the skin along the dorsal midline just posterior to the end of the rib cage. The skin was pulled laterally and a second incision was made through the musculature of the peritoneum. The adrenal was removed from the area anterior to the kidney using fine forceps. The incision was closed using surgical thread. The skin was then pulled to the other side and the procedure was repeated to remove the other adrenal gland. Before the initial incision was closed with surgical staples, a pellet containing either cholesterol or cholesterol plus CCS was inserted subcutaneously near the nape of the neck. The animals were adrenalectomized before pellet implantation because previous experience had demonstrated that plasma CCS levels were more stable when this procedure was done. Following surgery, animals were individually housed and provided with food and 0.9% saline drinking solution. All testing occurred 8 days following surgery. This time period was chosen because maximal changes in α-BTX binding occur by this time (Stitzel et al., 1996).

2.4. Nicotine administration

In both the PPI and auditory gating studies, animals were administered nicotine (Sigma) at a dose of 1 mg/kg (free base). The pH of the solution was adjusted to 7.2–7.4 before injection. This dose of nicotine has been shown to improve auditory gating in the DBA/2 model of abnormal auditory gating (Stevens and Wear, 1997).

2.5. Startle and PPI testing

The startle chamber (SR-LAB, San Diego Instruments, San Diego, CA) was housed in a sound-insulated box with a 66-dB ambient noise level. The chamber consisted of a ventilated Plexiglas cylinder 3.9 cm in diameter that rested on a 20.4×12.7 cm Plexiglas frame. Background and startle white noise bursts were presented through a Realistic speaker (model #40-1278B with frequencies predominantly between 5 and 16 kHz) mounted 12 cm above the animal. Sound levels were calibrated and measured with a Realistic digital sound level meter. Magnitude of the startle response was measured by a response transducer contained in the enclosure base on which the Plexiglas frame rested. Readings (1 ms) were collected beginning at stimulus onset, and the startle amplitude was defined as the average of 50 readings. For a detailed description of the response transducer, see Swerdlow and Geyer (1993). When calibrated with a "dynamic" standardization kit purchased from San Diego Instruments, the two chambers used for testing gave similar average readings of 780 over a 250 ms window.

To assess startle and PPI, mice were placed in the startle chamber for a 3-min acclimation period with a background noise level of 70 dB. After the acclimation period, mice were exposed to two types of trials: (1) a 20-ms acoustic white noise burst alone (90–120 dB in increments of 5 dB) and (2) a 20-ms prepulse white noise burst 100 ms prior to a 120-dB white noise acoustic startle stimulus. The prepulse intensity ranged from 75 to 95 dB in 5 dB increments. There were 12 different trial types for a total of 48 trials per test session. The intertrial interval was 10 or 15 s. The trials were arranged in pseudorandom order.

On the first day, animals received no injection prior to startle testing. On day 2, animals were injected with nicotine (1.0 mg/kg ip, as free base) and placed immediately into the startle chamber to acclimate as described above.

2.6. Recording of auditory gating

For electrophysiological recording of auditory gating, the mice were anesthetized with chloral hydrate (400 mg/kg ip) and pyrazole (400 mg/kg ip) to retard the metabolism of the chloral hydrate. The mice were placed in a mouse adaptor (Neuroprobe, Cabin John, MD) for the Kopf stereotaxic instrument (Kopf Instruments, Tujunga, CA). Hollow ear bars were placed adjacent to, but not inserted into, the auditory meatus and a heating pad maintained body temperature. Anesthesia was supplemented periodically to maintain absence of the reflexive withdrawal from toe pinch.

A burr hole in the skull was opened over the CA3 region of the hippocampus, and a tungsten microelectrode, impedance 8–10 MΩ at 1000 Hz, was inserted into the CA3 pyramidal layer of the hippocampus. The location of the electrode was estimated by its depth from the brain surface with final location identified by the presence of complex action potentials typical of hippocampal pyramidal neurons. The electrical activity was amplified 5000 times with bandpass 1–500 Hz and led to an analog to digital converter (RC Electronics, Bakersfield, CA) for averaging by computer.

Tones (300 Hz, 10 ms, 70 dB SPL) were presented in pairs, with a 0.5-s intrapair interval and 10 s between pairs. Responses to 16 pairs were averaged at 5-min intervals. The maximum negativity between 20 and 60 ms after the first stimulus was selected as the N40 wave and measured relative to the preceding positivity, a P20 wave. This particular complex has greater reproducibility for repeated measurements than either component alone (Cook et al., 1968). Three parameters were measured: conditioning amplitude — the magnitude of the response to the first, or conditioning, stimulus; test amplitude — the magnitude of the response to the second, or test, stimulus; and TC ratio — the ratio of the test amplitude/conditioning amplitude. A TC ratio less than 1 is indicative of suppression or inhibition of the response to the test stimulus (Andersen et al., 1964). A TC ratio of 0.4 or less is evidence of normal sensory inhibition (Miller and Freedman, 1995). After recording of three baseline records, nicotine (1 mg/kg sc, as free base)

was administered and records obtained at 5-min intervals, for 30 min.

2.7. Corticosterone radioimmunoassay

Immediately following behavioral testing, 50-μl venous blood samples were collected by retro-orbital sinus puncture to verify successful ADX and the level of glucocorticoid replacement. The CCS radioimmunoassay was performed using a kit obtained from ICN Pharmaceuticals (Costa Mesa, CA).

2.8. α-BTX binding

After the collection of blood samples that were used for the CCS assay, each animal was killed by cervical dislocation and its brain was removed and dissected into 10 brain regions: cerebellum, hindbrain, hypothalamus, cortex, hippocampus, striatum, thalamus, midbrain, inferior colliculi and superior colliculi. Brains were placed in 10 volumes of hypotonic ice-cold buffer (NaCl, 14 mM; KCl, 0.15 mM; $CaCl_2$, 0.2 mM; $MgSO_4$, 0.1 mM; HEPES, hemisodium salt, 2.5 mM; pH 7.5). Tissue preparation was similar to that of Romano and Goldstein (1980) as described in Marks et al. (1986).

The binding of [^{125}I]-α-BTX (Tyr-[^{125}I], initial specific activity, 211 Ci/mmol; Amersham, Buckinghamshire, UK) was performed at 37°C using the methods of Marks et al. (1986). All binding reactions were conducted in buffer of the following composition: NaCl, 140 mM; KCl, 1.5 mM; $CaCl_2$, 2 mM; $MgSO_4$, 1 mM; HEPES, hemisodium salt, 25 mM; 0.1% bovine serum albumin; pH 7.5. Single concentration assays were performed in each of the brain regions using 1.4-nM labeled toxin. The K_d for α-BTX binding to mouse brain is approximately 1 nM (Marks et al., 1986).

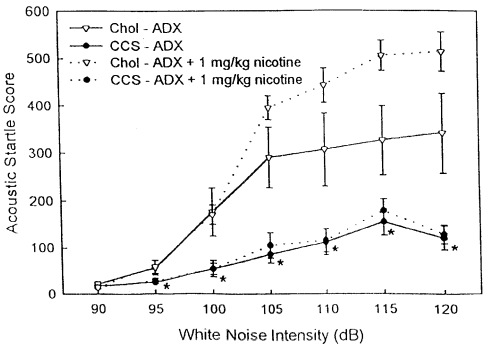

Fig. 1. Changes in acoustic startle response in adrenalectomized mice with either corticosterone (CCS–ADX) or cholesterol pellet (Chol–ADX) implantation (solid lines) and the results of nicotine administration (1 mg/kg ip) (dotted lines) to both groups of mice. CCS treatment produced a significant decrease in acoustic startle, which was unaffected by nicotine administration, whereas nicotine produced an increase in startle response in the cholesterol-treated mice. Data are mean ± S.E.M., $n = 10$ per group, * $P < .05$ compared to cholesterol-treated animals.

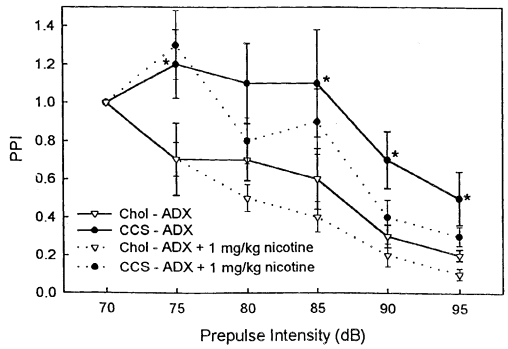

Fig. 2. Changes in PPI in adrenalectomized mice with corticosterone (CCS–ADX) or cholesterol pellets (Chol–ADX) (solid lines) and the effects of nicotine administration (1 mg/kg ip) (dotted lines) to both groups of mice. Elevated corticosterone produced a significant reduction in PPI as compared to the cholesterol-treated mice. Nicotine administration significantly improved PPI in both groups. Data are mean ± S.E.M., $n = 10$ per group, * $P < .05$ as compared to cholesterol-treated animals.

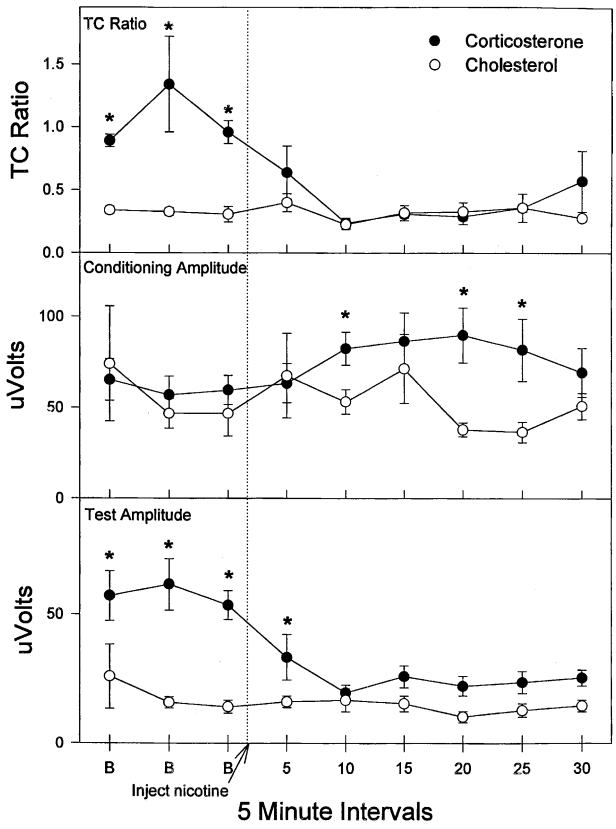

Fig. 3. The effects of chronic corticosterone pellet implantation, vs. cholesterol, on auditory gating parameters. Chronic corticosterone produced a significant increase in TC ratio, indicating a loss of auditory gating, at all three baseline time points, as compared to cholesterol-treated mice. The effect was solely through a significant increase in test amplitude. Administration of nicotine (1 mg/kg ip) to both strains of mice produced a significant improvement in auditory gating in the corticosterone-treated mice. From the first time point after injection, the corticosterone-treated mice were indistinguishable from the cholesterol-treated mice. The effect of the nicotine was primarily through a decrease in test amplitude, although there was some increase in conditioning amplitude. Data are mean ± S.E.M., $n = 10$ per group, * $P < .05$ as compared to cholesterol-treated mice.

2.9. Protein determination

Protein determinations were performed using the method of Lowry et al. (1951) with bovine serum albumin as the standard.

2.10. Statistical analyses

Statistical analysis of startle and PPI data did not include the first 12 trials to minimize the effects of habituation during the sessions analyzed (Bullock et al., 1997). PPI data were calculated as the average startle score recorded for 120 dB in the presence of an acoustic prepulse, divided by the average startle score (120 dB) alone for each individual animal. Analysis of variance was used to analyze startle scores as well as PPI ratios. Duncan's multiple range test was used to assess individual responses at each dB level. Auditory evoked potential data for adrenalectomized animals that received nicotine were analyzed by repeated measures ANOVA Tukey–Kramer a posteriori analyses were performed as required. Assessment of differences between CCS and control corticosterone levels was performed by Student's *t* test.

3. Results

As previously reported (Stitzel et al., 1996), ADX produced decreases in baseline corticosterone below that reliably detected in the assay used in this study. Following 8 days of corticosterone pellet treatment, corticosterone levels (596.5 ± 35.1 μg/dl) were significantly higher than levels in animals treated with cholesterol pellets (<25 μg/dl) ($t = 15.5$, $P < .001$).

In the startle and PPI studies, adrenalectomized C3H mice treated chronically with corticosterone produced startle scores that were significantly decreased [$F(1,91) = 164.9$, $P < .001$] across all decibel levels tested [95, 100, 105, 110, 115 and 120; $F(1,13) = 12.7$, 18.3, 31.6, 41.2, 30.4 and 38.0, respectively, $P < .005$] with the exception of 90 dB ($P = .62$), when compared to cholesterol-treated mice (Fig. 1). Interestingly, acute administration of nicotine enhanced startle in cholesterol-treated animals [$F(1,42) = 9.16$, $P = .004$], but not those treated with corticosterone [$F(1,49) = 1.33$, $P = .26$]. There were no significant effects of nicotine observed at individual decibel levels in the cholesterol-treated mice.

PPI was significantly decreased [$F(1,65) = 25.43$, $P < .001$] in corticosterone-treated animals compared to cholesterol-treated animals (Fig. 2). This decrease was due to an overall trend across all prepulse intensities as well as significant decreases at 75, 85, 90 and 95 dB [$F(1,13) = 7.38$, 4.71, 7.11 and 5.45, respectively, $P < .05$]. There was a significant overall increase in PPI, regardless of group, after administration of nicotine (1 mg/kg ip) [$F(1,65) = 9.94$, $P = .002$]. When each group was considered separately, nicotine also produced significant increases in PPI [cholesterol: $F(1,30) = 6.51$, $P = .02$; corticosterone: $F(1,35) = 5.30$, $P = .03$]. At individual prepulse intensities, nicotine's enhancement of prepulse inhibition was only significant at 95 dB for all pelleted animals [$F(1,13) = 5.49$, $P = .04$] and not significant at any decibel levels when the cholesterol and CCS animals were analyzed separately.

In the auditory-evoked potential paradigm, chronic treatment with corticosterone increased the TC ratio as compared to cholesterol-treated mice [$F(1,9) = 12.58$, $P = .006$]. This was accomplished by a significant increase in test amplitude

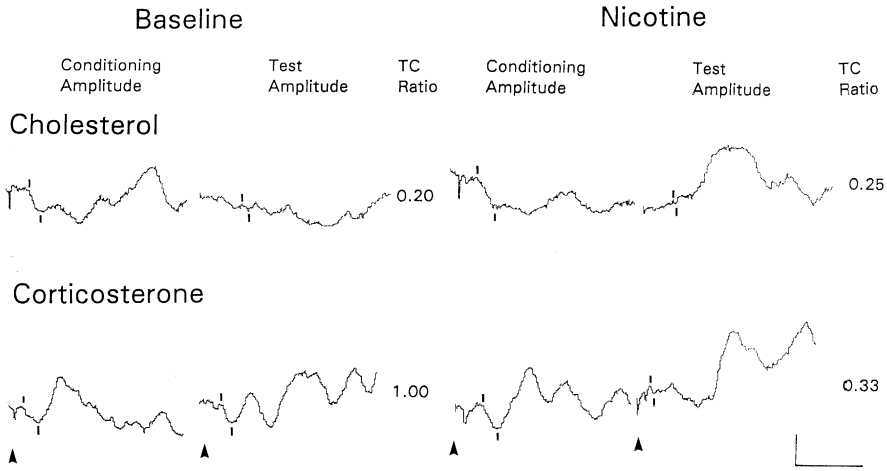

Fig. 4. Representative evoked potentials from adrenalectomized mice, which had cholesterol (control) or corticosterone pellet implantation. Records were made on the 8th day after pellet implantation. Tick marks denote the waveform of interest, stimulus onset is noted by the arrows. Cholesterol pellets had no effect on auditory gating as evidenced by the low TC ratio. In contrast, there was a loss of auditory gating in corticosterone-pelleted animals. Nicotine (1 mg/kg ip) had no effect in the cholesterol-treated mouse, but produced an improvement in gating in the corticosterone-treated mouse. Post nicotine data are 10 min after the injection. Calibration: 50 μV/50 ms.

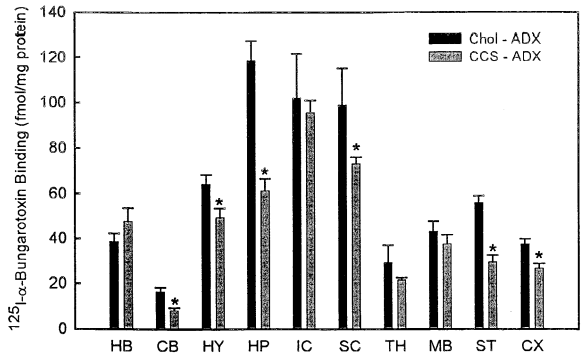

Fig. 5. Changes in α-BTX binding across brain areas in adrenalectomized mice with either cholesterol (Chol) or corticosterone (CCS) pellets. Chronically elevated corticosterone produced decreased α-BTX binding in the cerebellum (CB), hypothalamus (HY), hippocampus (HP), superior colliculus (SP), straitum (ST) and cortex (CT). No change was observed in the remaining structures (hindbrain, HB; inferior colliculus, IC; thalamus, TH; midbrain, MB). The largest reduction in α-BTX binding was observed in the hippocampus. Data are mean ± S.E.M., $n = 20$, $P < .05$.

[$F(1,9) = 18.19$, $P = .002$] with no change in conditioning amplitude [$F(1,9) = 2.33$, $P = .162$] (Figs. 3 and 4).

When nicotine (1 mg/kg, as free base) was administered to both groups, there was a significant interaction of corticosterone vs. cholesterol treatment and nicotine injection on TC ratio [$F(8,72) = 2.73$, $P = .025$] (Fig. 4). Nicotine produced a significant decrease in TC ratio in corticosterone-treated mice from 10 to 25 min after injection, as compared to preinjection baselines ($P < .05$), but had no effect on cholesterol-treated mice ($P > .05$). The improvement in auditory gating (decrease in TC ratio) was accomplished exclusively through a significant decrease in test amplitude in corticosterone-treated animals only [$F(8,72) = 2.98$, $P = .006$]. There were no significant changes in conditioning amplitude in either group of animals [$F(8,72) = 1.36$, $P = .230$].

Fig. 5 shows α-BTX binding in 10 brain regions for animals that were treated with either cholesterol or CCS. Binding differed significantly across regions [$F(9,86) = 65.3$, $P < .001$] and between pellet treatments [$F(1,86) = 49.1$, $P < .001$]. There was also a significant interaction between region and pellet [$F(9,86) = 6.12$, $P < .001$]. α-BTX binding differed between the cholesterol- and CCS-treated ADX animals in cerebellum, hypothalamus, hippocampus, superior colliculi, straitum and cortex ($P < .05$).

4. Discussion

These studies replicate previous work demonstrating a decrease in hippocampal α-BTX binding produced by elevated circulating corticosterone levels in C3H mice (Grun et al., 1995; Pauly and Collins, 1993; Pauly et al., 1988, 1990; Robinson et al., 1996; Stitzel et al., 1996). This effect was greatest in hippocampus, superior colliculus and straitum; no change was seen in other brain regions such as hindbrain, inferior colliculus and thalamus. CCS treatment also resulted in a decrease in auditory gating, acoustic startle and PPI. These results, coupled with the improvement in both paradigms with nicotine administration, suggest that a decrease in α-BTX binding may be associated with the change in behavior. Moreover, these results are consistent with the observations that mouse strain differences in auditory gating (Stevens et al., 1996), and acoustic startle and PPI (Bullock et al., 1997) are correlated with strain differences in hippocampal α-BTX binding; strains with low binding also had low auditory gating, startle and PPI. Thus, the assertion that gating is regulated by the number of hippocampal α-BTX binding sites is supported by studies using two totally different approaches.

The finding that alterations in α-BTX binding are accompanied by changes in gating stand in contrast to studies showing no change in PPI and auditory gating in α7 null mutant (Paylor et al., 1998, unpublished observations). As noted earlier, there are several possible explanations for failure to observe loss of putative α7-related behaviors in α7 null mutant mice. Studies have demonstrated triggering of compensatory changes following certain gene deletions (Dumartin et al., 2000; Fauchey et al., 2000). This is of particular interest with respect to α7 null mutant mice since the only documented consequences of deletion of this gene are the loss of α7 mRNA and α-BTX binding (Orr-Urtreger et al., 2000) suggesting some compensatory mechanisms have been initiated. Additionally, differences in expression due to genetic background have been noted (Homanics et al., 1997, 1998; Kelly et al., 1998). The α7 null mutant mice have been bred back to the C57BL/6 background. Work from our group has demonstrated altered behavioral responses to ethanol with the deletion of the PKCγ gene on a mixed 129-C57BL/6, while no changes are noted on the pure C57BL/6 background (Bowers et al., 1999, 2000). Either or both of these mechanisms could account for the failure to find differences in PPI and auditory gating in the α7 null mutant mice, without precluding mediation of these effects through the α7 nicotinic receptor.

Corticosterone elicits a broad array of biochemical and physiological changes. Consequently, it may be premature to conclude that the changes in gating evoked by CCS treatment are due solely to decreases in α-BTX binding. For example, elevated corticosterone has been linked to increases in dopaminergic neurotransmission (Barrot et al., 2000; Hall and McGinley, 1982; Iuvone et al., 1977; Piazza and Le Moal, 1996). Our own studies have shown that increased dopaminergic stimulation induces a loss of auditory gating (Stevens et al., 1996), while other groups have shown similar disruptions in PPI (Johansson et al., 1995; Mansbach et al., 1988). Thus, alterations in other systems induced by the elevated corticosterone may underlie the changes in gating seen in both paradigms.

Several studies have demonstrated that CCS treatment results in a decreased sensitivity to the effects of nicotine on locomotor activity and body temperature (Grun et al., 1995; Pauly and Collins, 1993; Pauly et al., 1988, 1990; Robinson et al., 1996). In concert with the present findings, chronic stress in rats produced a significant decrease in PPI, which was partially reversed by 6 mg/kg nicotine and fully reversed by 12 mg/kg nicotine (Acri, 1994; Faraday et al., 1999). The difference in species between the previous and current studies may explain the difference in nicotine dose (1 vs. 12 mg/kg) necessary to produce full reversal of the corticosterone-induced changes. Nicotine treatment resulted in an increase in acoustic startle in control (cholesterol-treated) animals and an increase in PPI. No effect of nicotine was observed on acoustic startle in the CCS-treated animals, but a significant improvement in PPI was noted. This finding suggests that the effects of nicotine on acoustic startle and PPI are modulated by the α-BTX binding site. In contrast, the effects of nicotine treatment failed to produce changes in the TC ratio in control C3H mice, but elicited a decrease in TC ratio in the corticosterone-treated animals. One possible explanation for this finding is that nicotine treatment activated nicotinic receptors other than the remaining α-BTX binding sites and that this activation reverses the loss of function in the absence of nicotine following CCS treatment. However, the improvement in auditory gating occurred primarily through a decrease in test amplitude, which is consistent with activation of α-BTX binding sites (Luntz-Leybman et al., 1992; Stevens and Wear, 1997; Stevens et al., 1998). While the exact mechanism underlying the effect on auditory gating is not clear, it is clear that CCS treatment does not produce decreases in sensitivity to all of nicotine's effects.

The present findings are also relevant to the study of the deficits found in schizophrenia. It has long been known that individuals with schizophrenia have poor auditory gating (Adler et al., 1982; Baker et al., 1987; Freedman et al., 1987) as well as poor PPI (Braff et al., 1992, 1995; Parwani et al., 2000). This deficit in inhibitory processing is thought to be based on abnormalities in the nicotinic cholinergic system (Adler et al., 1998; Freedman et al., 1994, 1995b). Specifically, studies have shown a significant reduction in hippocampal α-BTX binding in the post-mortem brains of schizophrenics as compared to matched controls (Freedman et al., 1995a). Other studies have demonstrated transient improvement in auditory gating among schizophrenics with nicotine administration (Adler et al., 1993). Most recently, genetic analysis of families with multiple incidences of schizophrenia has linked the gating deficit to chromosomal site 15q14, the site of the nicotinic α7 receptor (Freedman et al., 1997). These studies are in concert with the present data, and taken together, the human and mouse studies lend support to the theory that reduced hippocampal α7 receptors may underlie the sensory processing deficits observed in schizophrenia.

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