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Role of Serotonin in the Nicotine-Induced Depression of the Brainstem Auditory Evoked Response

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BHARGAVA, V., A. SALAMY AND S. SHAH. *Role of serotonin in the nicotine-induced depression of the brainstem auditory evoked response.* PHARMAC. BIOCHEM. BEHAV. 15(4) 587–589, 1981.—We have examined the role of serotonergic and/or dopaminergic mechanism in the mediation of the nicotine-induced depression of brainstem auditory evoked responses (BAER) to auditory stimuli. Nicotine produced dose- and time-dependent decreases in BAER amplitude. Administration of serotonin-depleting drugs (reserpine or p-chlorophenylalanine (PCPA)), prevented this decrease. Administration of catecholamine-depleting drugs (α-methyl-p-tyrosine, disulfiram or Dopa), on the other hand, had no effect. These data thus suggest a role for serotonergic mechanisms in the mediation of nicotine-induced depression of the brainstem auditory pathway.

Brainstem auditory evoked response Role of serotonin Nicotine-induced depression

OUR recent studies have provided evidence for the presence of cholinergic and serotonergic mechanisms in the modulation of brainstem auditory evoked responses (BAER) in the auditory pathway [2–4]. Nicotine produces a significant decrement in the amplitudes of BAER waves III and IV [1,4]. Domino [5] has presented evidence that the EEG activation and behavioral effects of nicotine are associated with the release of serotonin (5HT). The release of 5HT appears to be mediated through one or more of the Na^+-dependent reuptake systems within the serotonergic pre-synaptic membrane [6]. Furthermore, serotonin, noradrenaline, dopamine, GABA and glycine have been shown to inhibit unit activity following iontophoretic application to the cochlear nucleus, inferior colliculus and medial geniculate nucleus [8–10]. The present experiments were conducted, therefore, to determine the role of serotonergic and dopaminergic mechanisms in the mediation of the nicotine-induced depression of the BAER.

METHOD

Adult Sprague-Dawley male rats (200–300 g) bred in our colony were anesthetized with α-chloralose (65 mg/kg, IP). Auditory evoked responses were recorded using Grass E2 platinum needle electrodes inserted subcutaneously at the vertex of the scalp while the reference was placed at the anterior border of the pinna of the stimulated ear. The auditory stimuli, clicks (60 dB above experimenter's threshold) produced by Grass S4 stimulator, were delivered monaurally at the rate of 6/sec through a miniature receiver (M-98 Radioear) connected to a plastic tube fitted snugly into the ear canal. Bioelectric activity was led into a Grass P511 preamplifier set at 10–3000 Hz bandpass (1/2 amplitude range). An average of 400 FFPs to acoustic stimuli were summated on a P/8E (Digital Equipment Corp.) computer and written out on an X-Y plotter (Hewlett-Packard). A constant body temperature (35–36 °C) was maintained by keeping the animal on a heating pad; rectal temperature was monitored through the experiment. The level of significance was determined by using *t*-test for dependent measures.

The following drugs were administered intraperitoneally (IP): (1) nicotine; (2) reserpine; (3) p-chloro-phenylalanine (PCPA); (4) α-methyl-p-tyrosine; (5) disulfiram; and (6) L-dopa, obtained from Sigma Chemical Co. (St. Louis, MO).

RESULTS AND DISCUSSION

A typical BAER within 5 msec of the auditory stimuli consisted of four positive waves. The average peak latencies in adult animals were 0.95±0.02, 1.78±0.02, 2.58±0.02 and 3.55±0.02 msec (n=100 animals), respectively. Representative time-dependent changes in the BAER amplitude (measured from peak to preceding valley) are shown in Fig. 1. The effect of nicotine was apparent within 20 min of its administration, was maximal at about 60 min and lasted for more than 3 hr. Nicotine (12.5, 25, 50 and 100 μg/kg) produced a dose-dependent decrease in the amplitudes (Fig. 2). In accord with our earlier findings [4] and the observations of

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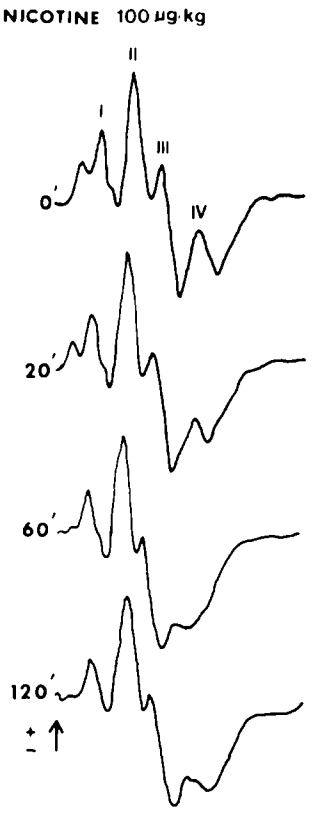

FIG. 1. The time course of BAER changes after administration of nicotine (100 µg/kg).

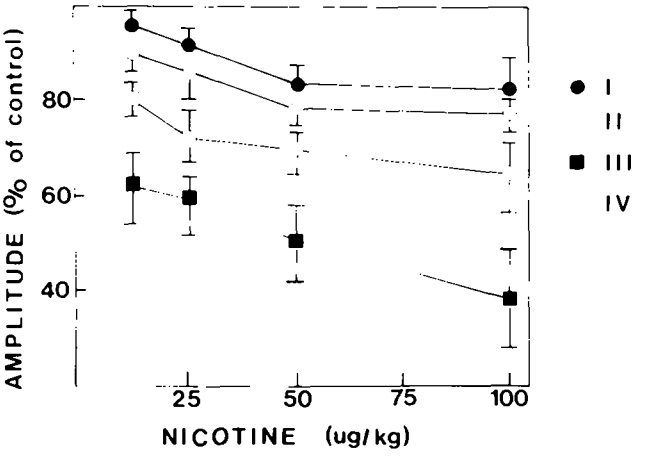

FIG. 2. The effect of various dosages of nicotine (12.5, 25, 50 and 100 µg/kg) on BAER amplitudes. Each point represents a mean of at least 4–6 animals (±SEM). The values are % change 60 min after the administration of nicotine.

Achor [1] this effect was most prominent on waves III and IV ($p<0.001$ and <0.025, respectively).

Pre-treatment with reserpine (5 mg/kg) 24 hr prior to testing blocked the characteristic nicotine-induced decrement of response amplitude (Table 1). To determine whether the blocking of the nicotinic effect might result, at least in part, from the decreased serotonergic activity, animals were pretreated with PCPA, which depletes the neurons of brain of serotonin more selectively than reserpine [7]. Similar to reserpine, PCPA also blocked the decremental effects of nicotine on BAER amplitude (Table 1).

In order to study the role of catecholamines on the BAER, the effects of α-methyl-p-tyrosine (250 mg/kg, 2 hr; n=30) or disulfiram (50 mg/kg, 2 and 12 hr treatment; n=5, each) catecholamine-depleting drugs on BAER were examined. These drugs failed to modify the BAER. Administration of L-dopa (100 mg/kg and 500 mg/kg, 2 and 12 hr treatments; n=6, each) also failed to produce a significant change in BAER.

Our results show that reserpine or PCPA (serotonin-depleting drugs) eliminates the decrease in BAER amplitude caused by nicotine. This blockade of the nicotinic response by reserpine or PCPA is comparable to that of mecamylamine, a specific nicotinic antagonist [4]. Thus, nicotine-induced inhibition appears to be mediated through not only cholinergic mechanism, but also through serotonergic intermediaries. Support for the role of serotonin in modulating BAER response also comes from our previous findings [2]

TABLE 1

NICOTINE EFFECT ON BAER AMPLITUDES AND ITS ELIMINATION BY RESERPINE AND PCPA

Drug	No. Animals	% Change (±SEM) I	II	III	IV
Nicotine*	10	−18.6 (±10.7)	−30.4 (±11.5)	−64.2 (±10.5)§	−35.6 (±6.9)§
Reserpine† + Nicotine*	10	+ 1.2 (±3.2)	+ 1.67 (±5.7)	+18.6 (±18.5)	+12.4 (±7.8)
PCPA‡ + Nicotine*	10	+15.9 (±24.8)	+ 6.0 (±9.9)	+18.6 (±17.4)	+20.7 (±21.7)

Results are expressed as % change 1 hr after the administration of nicotine.
*Nicotine 100 µg/kg IP (maximum effect).
†Reserpine 5 mg/kg, 24 hrs prior to experiment.
‡PCPA 25 mg/kg twice a day for 3 days prior to experiment.
§Significant at $p<0.05$ as determined by t-test for dependent measures.

where depletion of 5HT by PCPA increased the BAER amplitudes, while an increase in 5HT by administration of 5HTP resulted in a decrement of BAER amplitudes. Catecholamines seem to have no important role in FFP modulation, since administration of α-methyl-p-tyrosine, disulfiram or L-dopa at the dosage tested, did not modulate the BAER. Our study thus provides evidence for the role of serotonergic mechanism in the nicotine-induced depression in the brainstem auditory pathway.

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