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Increased Cardiovascular Responsiveness to Central Cholinergic Stimulation in the Genetically Epilepsy-prone Rat

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Abstract—We sought to determine whether differences in cardiovascular responsiveness to central stimulation of the cholinergic system existed between the genetically epilepsy-prone and outbred Sprague-Dawley rats. We treated the unanaesthetized, restrained rats with the indirect cholinergic agonist physostigmine (25, 50, 100 and 200 $\mu g\ kg^{-1}$, i.v.) and the direct muscarinic agonist arecoline (50, 100 and 200 $\mu g\ kg^{-1}$, i.v.). Blood pressure and heart rate were evaluated. Genetically epilepsy-prone rats demonstrated to be more susceptible to the action of physostigmine than the outbred Sprague-Dawley rats. Conversely, we did not note any difference between the two strains in the extent of the pressor response induced by arecoline. Moreover, we treated both strains with hemicholinium-3 (34·8 nmol, i.c.v.) to deplete endogenous stores of acetylcholine. This treatment did not affect the pressor response to arecoline, whereas it greatly reduced the response to physostigmine. The present results support an increased cardiovascular responsiveness to central cholinergic stimulation in the genetically epilepsy-prone rat which appears to be related to a pre-synaptic rather than a post-synaptic component.

The genetically epilepsy-prone rat represents a genetic model of epilepsy, developed by selectively inbreeding Sprague-Dawley rats that elicited a particular susceptibility to audiogenic stimulation (Jobe et al 1973; Reigel et al 1986). These rats respond with generalized clonic-tonic convulsions on exposure to a loud tone. Moreover, this strain shows a reduced seizure threshold for different electrical stimuli and elicits an enhanced susceptibility to convulsions induced by the administration of several convulsants (Dailey et al 1989).

Pharmacological activation of central cholinergic neurons is known to evoke a pressor response in several animal species including man (Brezenoff & Giuliano 1982; Buccafusco & Brezenoff 1986). This pressor response does not appear to be mediated by peripheral factors since only those cholinergic agonists that readily cross the blood-brain barrier possess the capability of producing a pressor response after systemic administration. For example, animals systemically pretreated with atropine methylbromide (to block selectively the peripheral effects of muscarinic stimulation) responded to the intravenous administration of direct muscarinic agonists, such as arecoline and oxotremorine, with a pressor response accompanied by an increase in heart rate (Makari et al 1989). Conversely, charged cholinesterase inhibitors, such as neostigmine and echothiophate, fail to induce a pressor response when administered systemically (Eickstedt et al 1955; Varagic 1955; Hornykiewicz & Kobinger 1956; Varagic & Beleslin 1962), whilst they increase blood pressure when administered into the cerebral ventricular system (Eickstedt et al 1955; Hornykiewicz & Kobinger 1956; Brezenoff 1972; Buccafusco & Brezenoff 1978).

With these concepts, we designed the present study to investigate whether differences in the cardiovascular responsiveness to central cholinergic stimulation exist between genetically epilepsy-prone and normotensive Sprague-Dawley rats. This phenomenon may be relevant considering that the site of action of intravenously administered physostigmine seems to be located in the lower brainstem (Brezenoff & Rusin 1974; Punnen et al 1986), and that this region appears to play a pivotal role in mediating the convulsive phenomena in the genetically epilepsy-prone rats (De Sarro & De Sarro 1991). This was expected to give us information on the possible difference in the cholinergic transmission between the two strains of rats.

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Materials and Methods

Animals

The genetically epilepsy-prone rats used for this study were inbred at the animal facilities of the Institute of Pharmacology at the University of Messina. Our colony derives from progenitors originally selected at the University of Arizona and then raised by Dr Brian S. Meldrum at the University of London, UK. We also used male, age-matched outbred Sprague-Dawley rats purchased from Charles-River, Calco, Como, Italy. All rats were housed three per cage in stable conditions of humidity (55 ± 5%), temperature (22 ± 1°C) and in a naturally occurring photoperiod. The animals had unlimited access to standard laboratory rat chow (MIL, S. Morini, S. Polo D'Enza, RE, Italy) and tap water. All animals used in the present study were male and of 12–13 weeks of age.

Genetically epilepsy-prone rats were tested three times at weekly intervals between the 6th and the 8th week of their life. The rats showing a complete audiogenic seizure in all three exposures to sound stimulation were considered audiogenic seizure-susceptible (GEP+), whereas eight rats that failed to exhibit seizures during 60 s of continuous audiogenic stimulation at each of the three times were selected as audiogenic seizure-resistant (GEP−). Seizures were induced

by exposing the animals to a mixed frequency sound (12–16 kHz) of 109 dB intensity under a hemispheric plexiglass dome (58 cm diam.) for 60 s. We considered a full seizure response as one or two running phases followed by a convulsion as previously described in detail (De Sarro et al 1989).

Surgical procedures

Rats were anaesthetized with diethyl ether and a catheter (PE50) filled with saline/heparin (20 units mL^{-1}) was inserted into the left femoral artery. A second catheter was implanted in the right jugular vein and exteriorized at the nape of the neck to permit the intravenous injection of drugs. Animals were then restrained on a soft polystyrene support and were allowed about 180 min to recover from the anaesthesia before the first recording of blood pressure. Arterial pressure was recorded in unanaesthetized, restrained rats by connecting the arterial line to a Keller pressure transducer (Winterthur, Switzerland) coupled to a Gemini 7070 polygraph recorder (U. Basile, Comerio, Varese, Italy). Heart rate was measured by a cardiotachometer triggered from the blood pressure pulses. Blood pressure and heart rate were recorded for at least 20 min or until a stable reading was obtained.

Experimental procedures

Animals of the three groups (Sprague-Dawley, GEP+, GEP−) were treated with three increasing intravenous doses of arecoline (50, 100, 200 $\mu g\ kg^{-1}$) and with four doses of physostigmine (25, 50, 100, 200 $\mu g\ kg^{-1}$) by the same route. Rats given arecoline were pretreated with intravenously-injected methylscopolamine (0·65 $mg\ kg^{-1}$, 20 min before the drug injection) to avoid the peripheral effect of the compound. Conversely, no muscarinic blocking drugs were administered to the animals that received physostigmine, since peripheral inhibition of cholinesterase results in no significant peripheral cardiovascular response. Each rat was given increasing doses of the same drug, allowing enough time for the blood pressure to return to baseline levels between each dose. No animal received more than one cholinergic agonist. To determine the extent to which the pressor response to each agonist depended upon the release of endogenous acetylcholine, we injected Sprague-Dawley and GEP+ rats intracerebroventricularly with hemicholinium-3 to deplete brain stores of acetylcholine (Finberg et al 1979). For this purpose rats were anaesthetized with ketamine (150 $mg\ kg^{-1}$, i.p.) and were permanently implanted with a stainless steel cannula directed at the right lateral cerebral ventricle as previously described (Trimarchi et al 1986). Animals were housed separately for at least eight days to recover before undergoing the subsequent surgical procedures. On the day of the experiment, the rats underwent the vascular surgery as described earlier in this section. After a 180-min recovery period, each animal received intravenously either arecoline or physostigmine (100 and 200 $\mu g\ kg^{-1}$) and blood pressure and heart rate were recorded. When the blood pressure and heart rate returned to normal values, hemicholinium-3 (34·8 nmol) was administered into the right cerebral ventricle through the implanted cannula and 60 min was allowed for depletion of acetylcholine in brain. Then, the cholinergic agonist was again administered and blood pressure and heart rate measured. No animal received more than one injection of hemicholinium-3 and animals so treated were not used for subsequent experiments.

Another group of Sprague-Dawley and GEP+ rats were injected intracerebroventricularly with 20 nmol physostigmine through an intracranial cannula implanted using the surgical procedures described above. In this last group blood pressure and heart rate were recorded as earlier indicated.

Statistics

Values are presented as mean ± s.e.m. Comparisons between means of several populations were performed using analyses of variance. The differences between means of two groups were estimated using Student's *t*-test for unpaired data. A probability $P < 0{\cdot}05$ was considered to indicate a significant difference.

Drugs

Drugs administered intravenously, were given over a period of 15 s through the catheter inserted in the jugular vein. Arecoline hydrobromide was obtained from ICN Biomedicals SpA, Cassina de'Pecchi, Milan, Italy, and scopolamine methyl bromide (methylscopolamine), eserine emisulphate (physostigmine) and hemicholinium-3 were purchased from Sigma Chimica, Milan, Italy. All drugs were dissolved in 0·15 M NaCl (saline) and the doses are expressed as the respective salts.

Results

The effects of the intravenous administration of arecoline

Arecoline given intravenously (50–200 $\mu g\ kg^{-1}$) in the methylscopolamine-pretreated rats, produced a dose-related increase in blood pressure (Fig. 1). No significant difference in the pressor response induced by intravenous arecoline among the three considered groups of rats was evident.

Arecoline also increased heart rate; however, the magnitude of the response was variable and not related to the dose. The maximal change in heart rate was observed at the dose of 100 $\mu g\ kg^{-1}$ in the GEP+ and GEP− rats (41·6 ± 10·4 and 35 ± 11·6 beats min^{-1}, respectively) and at the dose of 200 $\mu g\ kg^{-1}$ (38·1 ± 10·9 beats min^{-1}) in the Sprague-Dawley rats.

The time-course of the increase in systolic pressure of arecoline (200 $\mu g\ kg^{-1}$, i.v.) in the three groups is illustrated in Fig. 2. The pressor response to arecoline reached a maximum 1 min after injection and returned to basal levels within 10 min. Again, no significant differences between the entire curves derived from GEP+ and Sprague-Dawley rats were statistically evident. The small number of audiogenic seizure-resistant rats that we were able to select did not allow us to do the same statistical analysis between them and the other two groups. It appears clear, however, that no differences were detectable between the time-course of the pressor response to arecoline in the GEP− group with respect to both Sprague-Dawley and GEP+ (Fig. 1).

The effects of the intravenous administration of physostigmine

Intravenous injection of physostigmine evoked a pressor response of greater magnitude in the GEP+ and GEP− as compared with Sprague-Dawley rats. Fig. 3 represents the effects of the intravenous injection of four increasing doses

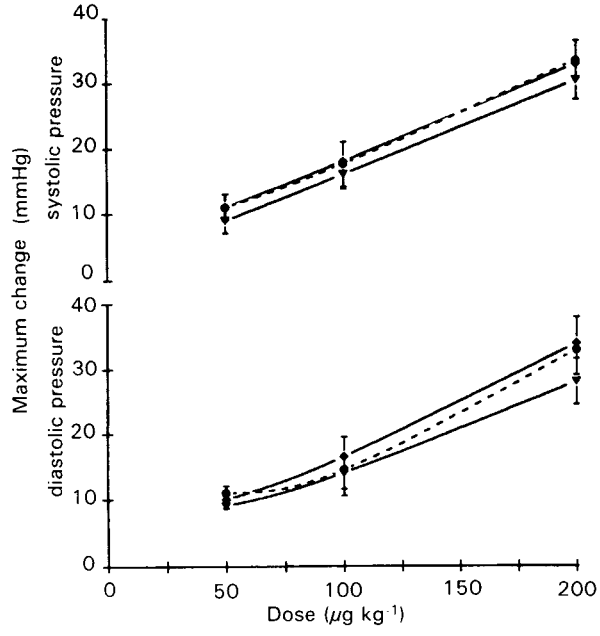

FIG. 1. Dose-pressor response relationship for arecoline in Sprague-Dawley (▼), GEP+ (◆) and GEP− (●) rats. All rats received 0·65 mg kg^{-1} methylscopolamine 20 min before arecoline injection. The maximum change with respect to pre-drug, resting blood pressure is plotted as a function of dose. Each value represents the mean of eight animals for the Sprague-Dawley and GEP+ groups and four animals for the GEP− group. Vertical lines show the s.e.m. Pre-injection levels of diastolic pressure in the Sprague-Dawley, GEP+ and GEP− rats averaged 107·6±6·7, 100·5±5·9 and 103·0±7·5 mmHg, respectively. For systolic pressure the same parameters were 156·1±6·0, 145·3±5·1 and 149·0±5·1, respectively.

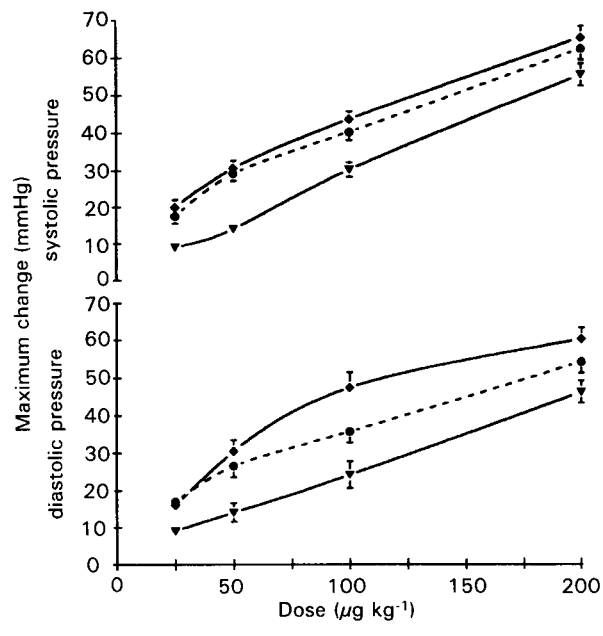

FIG. 3. Dose-pressor response relationship for physostigmine in rats. The maximum change with respect to pre-drug, resting blood pressure is plotted as a function of dose. Each value represents the mean of eight experiments for the Sprague-Dawley (▼) and GEP+ (◆) groups and four experiments for the GEP− (●) group. Note that in both GEP+ and GEP− rats the intravenous injection of physostigmine produced a more marked pressor response with respect to Sprague-Dawley rats. Pre-injection levels of diastolic pressure in the Sprague-Dawley, GEP+ and GEP− rats averaged 104·7±4·7, 104·7±5·2 and 106·3±8·1 mmHg, respectively. For systolic pressure the same parameters were 148·4±7·6, 145·3±6·7 and 146·9±7·9, respectively.

(25, 50, 100, 200 μg kg^{-1}) of the compound on systolic and diastolic pressure in the three groups of animals considered in this study. The GEP+ rats responded to physostigmine administration with a more pronounced pressor response with respect to Sprague-Dawley rats and this effect was statistically significant both for systolic and diastolic pressure ($F(1,56)=59·72$ and 51·98, respectively). Similarly, physostigmine produced an increase in systolic and diastolic pressure that was larger in the GEP− than in the Sprague-Dawley rats ($F(1,40)=28·24$ and 18·08, respectively). On the other hand, no statistically significant differences were recorded between the physostigmine-induced pressor responses in GEP+ and GEP− rats (Fig. 3). The time-course of the pressor response of 100 μg kg^{-1} physostigmine is presented in Fig. 4. The systolic pressure reached a maximum 4–5 min after the injection and returned to the pre-injection

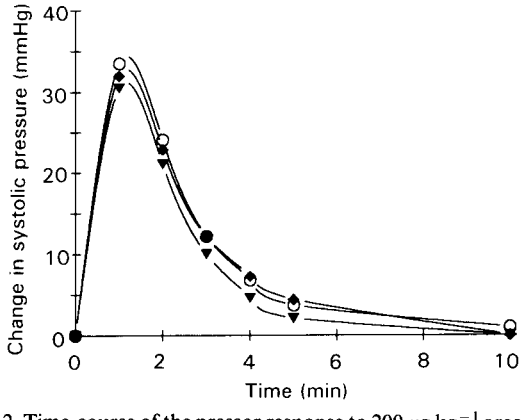

FIG. 2. Time-course of the pressor response to 200 μg kg^{-1} arecoline injected intravenously in rats. All rats received 0·65 mg kg^{-1} methylscopolamine 20 min before arecoline injection. Each value represents the mean of eight animals for the Sprague-Dawley (▼) and GEP+ (◆) groups and four animals for the GEP− (○) group.

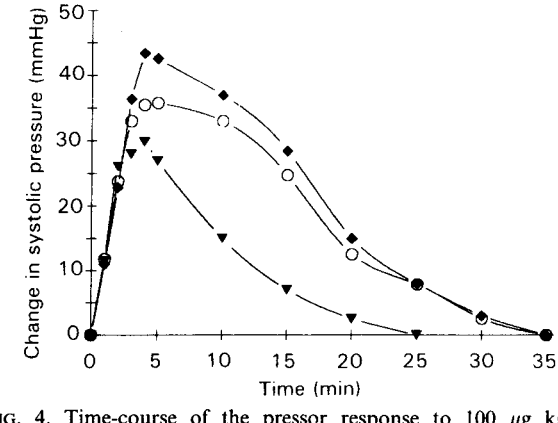

FIG. 4. Time-course of the pressor response to 100 μg kg^{-1} physostigmine injected intravenously in rats. Each value represents the mean of eight animals for the Sprague-Dawley (▼) and GEP+ (◆) groups and four animals for the GEP− (○) group. Note that the curve generated by GEP+ rats was statistically different from the one generated by Sprague-Dawley rats ($F(1,14)=48·66$; $P<0·0001$).

levels by 25 min for the Sprague-Dawley rats, whereas at least 35 min was needed for blood pressure to reach the basal level in both GEP+ and GEP− rats. Moreover, the entire curves derived from GEP+ were significantly greater than those derived from Sprague-Dawley rats ($F(1,14)=48{\cdot}66$ by means of analysis of variance for repeated measures). This phenomenon was also evident between GEP− and Sprague-Dawley rats, although due to the difference in the number of experiments between the two groups the statistical analysis was not performed.

Intravenous physostigmine also produced bradycardia in all rats showing no differences either in magnitude or in duration among the three strains. The maximal change in heart rate was observed at the dose of 200 μg kg^{-1} and averaged in GEP+, GEP− and Sprague-Dawley rats $-57{\cdot}25\pm5{\cdot}52$, $-57{\cdot}75\pm9{\cdot}14$ and $-48{\cdot}5\pm5{\cdot}91$ beats min^{-1}, respectively.

The effects of pre-treatment with hemicholinium-3 on the pressor response to intravenous injection of arecoline and physostigmine

To determine whether the pressor response to the two cholinergic agonists depended upon endogenous acetylcholine, the effect of pre-treatment with the acetylcholine-depleting agent, hemicholinium-3, administered intracerebroventricularly, on the evoked pressor responses was examined. These results are summarized in Table 1. Pre-treatment with hemicholinium-3 inhibited the pressor response to physostigmine by 53–75% in the Sprague-Dawley rats and 53–71% in the GEP+ rats. In contrast, the pressor response to arecoline did not appear significantly modified by hemicholinium-3 in either normotensive or genetically epilepsy-prone rats.

The effects of intracerebroventricular administration of physostigmine

To investigate whether the difference in the extent of the pressor response to intravenous physostigmine between Sprague-Dawley and GEP+ rats was attributable to a different rate of drug entry to the brain, we gave the compound directly into the lateral cerebral ventricle. The animals of both strains responded to intracerebroventricular physostigmine (20 nmol) with a pressor response of a greater magnitude and duration in the GEP+ rats than in the Sprague-Dawley rats, as indicated in Fig. 5. This treatment also induced a decrease in heart rate of a similar extent in the two groups of rats (-50 ± 10 and -49 ± 7 beats min^{-1} for Sprague-Dawley and GEP+ rats, respectively). The bradycardic effect of intracerebroventricular physostigmine, however, returned to pre-injection values within 20–25 min in the Sprague-Dawley group whereas 30–35 min were necessary in the GEP+ rats. We used the dose of 20 nmol since it was the highest that did not induce seizures in all the GEP+ rats tested.

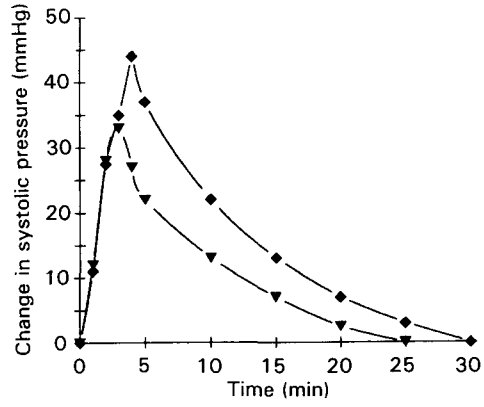

FIG. 5. Time-course of the pressor response to 20 nmol physostigmine injected into the right lateral cerebral ventricle in Sprague-Dawley (▼) and GEP+ (◆) rats. Each value represents the mean of eight animals. Note that the curve generated by GEP+ rats was statistically different from the one generated by Sprague-Dawley rats ($F(1,14)=101{\cdot}35$; $P<0{\cdot}0001$). Pre-injection levels in the Sprague-Dawley and GEP+ rats were $110{\cdot}9\pm7{\cdot}3$ and $106{\cdot}3\pm5{\cdot}3$ mmHg for diastolic pressure and $151{\cdot}6\pm6{\cdot}4$ and $148{\cdot}4\pm5{\cdot}5$ mmHg for systolic pressure, respectively.

Discussion

Over the last several years, few attempts have been made to investigate the implication of central cholinergic system alterations in the genetically epilepsy-prone rat. The present results show a marked difference between normal and genetically epilepsy-prone rats in the extent of the pressor response produced by activation of central cholinergic synapses. The pressor responses to intravenous administra-

Table 1. Effect of hemicholinium-3 on the increase in systolic pressure induced by intravenous injection of centrally-active cholinergic agonists.

Agonists (μg kg^{-1})	Sprague-Dawley		GEP+	
	Untreated	HC-treated	Untreated	HC-treated
Arecoline				
100	16 ± 2	18 ± 4	18 ± 4	14 ± 7
200	31 ± 4	36 ± 8	33 ± 4	34 ± 9
Physostigmine				
100	30 ± 2	14 ± 5*	43 ± 2	20 ± 6*
200	55 ± 3	14 ± 4*	65 ± 3	19 ± 6*

Hemicholinium-3 (HC) was injected intracerebroventricularly at the dose of 34·8 nmol 60 min before the intravenous injection of cholinergic agonists. Each value represents the mean maximal change in systolic pressure (mmHg) with respect to pre-agonist resting mean pressure. Values indicate the mean ± s.e.m. of eight experiments.
*Significantly different ($P<0{\cdot}05$) with respect to untreated rats.

tion of physostigmine, but not to arecoline, appears enhanced in GEP+ rats when compared with Sprague-Dawley rats. The mode of action of the two compounds considered in the present study differs in their site of action on the cholinergic neuron. In fact, whilst the intravenous administration of physostigmine produces its effect by increasing the availability of endogenously released acetylcholine, arecoline evokes cholinergic responses by a direct action on the muscarinic receptor. In this study, we used these two different cholinergic agonists in order to investigate whether the differences in the susceptibility to central cholinergic stimulation between genetically epilepsy-prone and normotensive rats were due to alterations in the pre- or post-synaptic component of the central cholinergic system. The fact that physostigmine induced a significantly greater pressor response in the genetically epilepsy-prone rat, whereas the responses produced by arecoline were of similar magnitude between the two strains, suggests that the difference in the blood pressure response was mainly due to an enhanced pre-synaptic activity in the cholinergic synapses that participate in cardiovascular regulation in the genetically epilepsy-prone rats. However, this view presupposes that both drugs act on the same cholinergic neuron. We cannot, in fact, rule out the possibility that the administration of either arecoline or physostigmine activates a cholinergic pathway that involves more than one cholinergic neuron, linked in series. To investigate this last point, we employed hemicholinium-3 as a tool to eliminate central pre-synaptic mechanisms in the action of each agonist. The increase in blood pressure in response to arecoline was not reduced by the pre-treatment with hemicholinium-3, thus the possibility that more than one cholinergic synapse is involved in the pressor response evoked by arecoline is excluded. Similar results have been recently described by Makari et al (1989) in spontaneously hypertensive rats. Furthermore, neurochemical study in spontaneously hypertensive rats suggested that a possible site of action of intravenously administered physostigmine appears to be located in the lower brainstem (Brezenoff & Rusin 1974; Punnen et al 1986; Trimarchi & Buccafusco 1987). Similarly, evidence has been presented which indicates that neurotransmitter function may be altered in different regions of the brainstem, known to modulate clonic-tonic seizures in genetically epilepsy-prone rats (Faingold et al 1986a, b; Millan et al 1986; De Sarro & De Sarro 1991). The observed bradycardic effect of physostigmine (when injected either intravenously or intracerebroventricularly) has been extensively reported by different laboratories and is likely to be produced via an increase in vagal tone to the heart (Buccafusco & Brezenoff 1979; Makari et al 1989). Conversely, in the arecoline-treated rats pre-treatment with methylscopolamine, just by blocking the vagal response, masked the effects of the compound on heart rate. However, it has to be considered that, for reasons still not clear, the activation of central muscarinic receptors by direct agonists has been reported to induce changes in heart frequency variable in both magnitude and direction (Brezenoff & Giuliano 1982).

Recently, our group reported a significant enhancement of the blood-brain-barrier permeability in the genetically epilepsy-prone rat in comparison with normal Sprague-Dawley rats (Saija et al 1992). In the light of this evidence it could be suspected that the differences in the magnitude of the pressor response evoked by intravenous administration of cholinergic agonists have to be related more to an increased amount of drug reaching the brain rather than to an increased neuronal susceptibility to the effects of the compound. However, only physostigmine produced a more marked increase in arterial blood pressure in GEP+ rats compared with Sprague-Dawley rats; thus we have to conclude that in the GEP+ rats the rate of entry to the brain was altered only for physostigmine and not for arecoline. The injection of physostigmine directly into the cerebral ventricle produced a pressor response that was more marked and prolonged in the GEP+ than in Sprague-Dawley rats, confirming an increased neuronal sensitivity to the compound in the genetically epilepsy-prone rats.

Another aspect that should be considered in discussing the results of the present study is that no significant difference in the cardiovascular responses to cholinergic stimulation between GEP+ and GEP− rats has been observed. It appears that the increased central cholinergic reactivity has no relation to sound-induced clonic-tonic convulsions. However, although GEP− rats are not susceptible to audiogenic seizures, they maintain an enhanced susceptibility to several convulsant treatments, i.e. aminophylline, pentetrazol (personal observation). Moreover, it has been recently reported that genetically epilepsy-prone rats present a reduced rate of cerebral uptake of glucose in comparison with normal Sprague-Dawley rats and, in analogy with our observation on the cardiovascular responses, this abnormality appears to be present in both GEP+ and GEP− rats (Saija et al 1992).

Our data strongly support an alteration in the neuronal activity through certain cholinergic pathways in the brain of genetically epilepsy-prone rats. This alteration is most likely to be related to modifications in the pre-synaptic rather than the post-synaptic components.

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