Cardiovascular responses to electrical stimulation of the septum in the rat

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Calaresu, Franco R., and Gordon J. Mogenson. Cardiovascular responses to electrical stimulation of the septum in the rat. Am. J. Physiol. 223(4): 777-782, 1972.—Cardiovascular responses to electrical stimulation of histologically verified sites in the septum were studied in 60 rats. In animals under α-chloralose anesthesia stimulation of the lateral septum (24 sites) elicited arterial hypertension, stimulation of the medial septum (19 sites) elicited arterial hypotension, and stimulation of an intermediate zone between the two areas (10 sites) elicited hypertension followed by hypotension. In contrast to these results, in animals under urethan anesthesia stimulation of the lateral septum (22 sites) elicited arterial hypertension and stimulation of the medial septum (10 sites) elicited arterial hypotension. In addition, on 10 occasions, stimulation of the lateral septum in animals under urethan elicited a hypertension accompanied by rhythmic oscillations of arterial pressure at a frequency of 24.6 ± 0.2/min. In all animals stimulation of the septum did not elicit significant changes in heart rate but produced an increase in the frequency of respiration. The cardiovascular responses observed in animals under both anesthetics were not altered by the administration of tubocurarine. The optimal parameters of stimulation were found to be pulses of 2 msec duration at 80 Hz. It is concluded that the septum plays a very complex role in the central control of the cardiovascular system as indicated by the findings of two distinct and opposite responses in two different areas of the septum and by the reversal of the responses in animals under two different anesthetics.

METHODS

Results were obtained in 60 male Wistar albino rats weighing 230–410 g; 26 were anesthetized with α-chloralose (15 mg/100 g, injected intravenously into the lateral caudal vein) and 34 were anesthetized with urethan (120 mg/100 g ip). A tracheal cannula was inserted; arterial pressure, monitored by a Statham transducer connected to a catheter in either femoral artery, and respiration, monitored as a change in temperature of tidal air by a thermistor in the tracheal cannula, were recorded on a Grass 7 polygraph. The rectal temperature of the animals was kept at 38 C ± 0.2 by the use of a heating blanket controlled by a Yellow Springs Instrument Co. model 73 temperature controller.

Stimulation of septum. The heads of the animals were fixed in a Kopf stereotactic instrument and selective electrical stimulation of the septum was done with SNEX-100 coaxial bipolar stainless steel electrodes (Rhodes Instruments, Los Angeles, Calif.). The electrodes were placed according to stereotaxic coordinates 1–3 mm anterior to the bregma, up to 1.2 mm lateral to the midline, and 4–8 mm below the
surface of the skull (19). The electrodes were connected to a Grass S4E stimulator. To determine optimal parameters of stimulation, pulse duration and frequency were altered in selected experiments: the parameters that were found to elicit maximal responses were a duration of 2 msec, a frequency of 80 Hz, and an amplitude of 10–13 v. The stimulus was therefore a 10- to 30-sec train of rectangular pulses at 80 Hz, 2 msec, and 10–13 v. Accurate histological localization of the electrode tips was obtained by placing, from the central lead of the electrode, iron deposits, which were later detected by a method previously described (3). In an additional series of 12 rats (6 under chloralose and 6 under urethan) the effect of administration of tubocurarine on the cardiovascular responses elicited by septal stimulation was investigated. The animals were given artificial respiration and tubocurarine (tubocurarine chloride injection; Abbott Laboratories, Montreal, Can.; 75 μg/kg) was administered into a cannulated femoral vein to stop spontaneous respiration.

Analysis of data. Heart rate was calculated from systolic arterial pressure peaks and respiratory rate from expiratory peaks in the 10 sec before the stimulus and in the last 5 sec of the train of stimulation. Mean arterial pressure responses were determined by adding one-third of the pulse pressure to the diastolic pressure during the peak of the response. Values of mean arterial pressure, heart rate, and respiratory frequency before and during stimulation were averaged from three runs obtained immediately before placing an iron deposit.

RESULTS

Animals anesthetized with chloralose. Selective electrical stimulation of 33 histologically identified sites in the septum of 14 animals in this series elicited cardiovascular responses which always appeared within 3 sec from the onset of stimulation, persisted during the duration of stimulation, and disappeared within 10 sec from the termination of stimulation. When the electrode was located in the lateral septum (24 sites), stimulation consistently elicited a significant decrease in arterial pressure. Mean respiratory frequency was significantly greater during stimulation, although this response was not found at all sites (an increase in 19 and a decrease in 5). The changes in heart rate were not statistically significant because of the inconsistent responses (a decrease in 12, no change in 11, and an increase in 1). A typical response of arterial pressure is shown in Fig. 1A. However, when the electrode was located in the medial septum (19 sites), the response was a consistent and significant increase in arterial pressure. Mean respiratory frequency was again significantly greater (an increase in 17 and a decrease in 2) and the changes in heart rate were not statistically significant (a decrease in 5, no change in 10, and an increase in 4). Finally, when the electrode was located at the border between medial and lateral septum (10 sites) the response was a consistent and significant increase in arterial pressure followed by a gradual decline terminating in a decrease in arterial pressure (Fig. 1C); heart rate and respiratory frequency showed no significant changes. These characteristic responses elicited by stimulation of the three anatomical locations were well illustrated in five animals in which it was possible to stimulate the lateral septum, the border area and then the medial septum in the same penetration (Fig. 2). A summary of the cardiovascular and respiratory responses elicited in animals under chloralose and a map of sites of stimulation are shown in Table 1 and Fig. 3. Two iron deposits in the medial and lateral septum are shown in Fig. 4.

Animals anesthetized with urethan. Selective electrical stimulation of 32 histologically identified sites in the septum of 22 animals in this series elicited cardiovascular responses with the same time course observed in animals under chloralose. Stimulation of the lateral septum (22 sites) consistently elicited a significant increase in arterial pressure; a significant increase in respiratory frequency (an increase in 10 and a decrease in 4) was again observed. Mean changes in heart rate were not statistically significant (an increase in 11, no change in 8, and a decrease in 2). A typical response is shown in Fig. 5A. On the other hand, stimulation of the medial septum (10 sites) consistently elicited a brief and slight increase in arterial pressure followed by a significant decrease of arterial pressure, no change in heart rate and a significant increase in respiratory frequency (Fig. 5B). A summary of the cardiovascular and respiratory responses elicited in the animals under urethan and a map of sites of stimulation are shown in Table 1 and Fig. 6.

In 10 animals under urethan anesthesia, when the stimulating electrodes were located in sites which were later identified histologically as being in the lateral septum, electrical stimulation consistently elicited the characteristic hypertensive response (from 112 ± 4 to 158 ± 5 mm Hg) with the addition that rhythmic oscillations in arterial pressure at a very consistent frequency (24.6 ± 0.2/min) were observed throughout the period of stimulation. In these animals there was no significant increase in heart rate but respiratory frequency was significantly increased (from 142 ± 10 to 207 ± 11/min, P < 0.01). A typical example of this response is shown in Fig. 5C.

Parameters of stimulation and cardiovascular responses. In view
TABLE 1. Changes in cardiorespiratory parameters elicited by septal stimulation

<table>
<thead>
<tr>
<th>Preparation and Location</th>
<th>MAP, mm Hg</th>
<th>HR, min⁻¹</th>
<th>RF, min⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>During</td>
<td>Change</td>
</tr>
<tr>
<td>Chloralose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lateral septum (n = 24)</td>
<td>122 ± 3</td>
<td>84 ± 4</td>
<td>-38 ± 5*</td>
</tr>
<tr>
<td>Medial septum (n = 19)</td>
<td>117 ± 4</td>
<td>145 ± 4</td>
<td>+28 ± 5*</td>
</tr>
<tr>
<td>Urethan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lateral septum (n = 22)</td>
<td>105 ± 3</td>
<td>147 ± 5</td>
<td>+42 ± 6*</td>
</tr>
<tr>
<td>Medial septum (n = 10)</td>
<td>104 ± 4</td>
<td>01 ± 5</td>
<td>-25 ± 6*</td>
</tr>
</tbody>
</table>

All values are means ± se; MAP = mean arterial pressure; HR = heart rate; RF = respiratory frequency. * P < 0.05. n = number of sites stimulated.

FIG. 2. Typical arterial pressure responses elicited by electrical stimulation of septum at different depths from surface of skull in a rat under chloralose. A: during stimulation of lateral septum (depth = 4.9 mm). B: during stimulation at border between medial and lateral septum (depth = 6.1 mm). C: during stimulation of medial septum (depth = 7 mm).

of the fact that in previous reports of cardiovascular responses to electrical stimulation of the septum the stimuli used were pulses of long duration (6), experiments were done in six animals under urethan and six under chloralose to study the effect of varying pulse duration and frequency of stimulation on cardiovascular responses. When a responsive site was found, stimuli were applied at frequencies of 1, 2, 5, 10, 20, 40, 80, and 160 Hz with a constant pulse duration of 2 msec, and at durations of 1, 2, 4, and 8 msec at a constant frequency of 80 Hz. The results obtained in six animals under urethan with stimulation of the lateral septum are shown in Fig. 7. It can be seen that maximum responses were obtained when the duration and frequency of the stimulus were 2 msec and 80 Hz, respectively. Similar experiments when the stimulating electrode was located in the medial and lateral septum in animals under chloralose and in the medial septum in animals under urethan confirmed the finding that 2 msec and 80 Hz were optimal parameters of stimulation to obtain cardiovascular responses.

FIG. 3. Location of placements of electrodes in sites in septum where electrical stimulation elicited arterial pressure responses in rats under chloralose. Arterial hypotension, ▲, arterial hypertension, ◀, arterial hypertension followed by hypotension. Transverse sections of brain are modified from a stereotaxic atlas (19). ACB = area lateral parolfactory; CA = anterior commissure; CC = corpus callosum; DBB = diagonal band of Broca; LS = lateral septum; MPO = area preoptica medialis; MS = medial septum; POA = area preoptica lateralis. Calibration in millimeters.
Iron deposits (indicated by arrows) at sites of stimulation in septum in transverse sections. A: a deposit in medial septum, thionin and potassium ferrocyanide stain, 50 μ-section. B: a deposit in lateral septum, Weil’s and potassium ferrocyanide stain, 50 μ-section. Calibration 1 mm.

Effect of administration of tubocurarine. As it has been suggested that electrical stimulation of central structures may elicit changes in arterial pressure and heart rate which are secondary to muscular activity induced by the stimulation (e.g., 8), and in view of the possibility that cardiovascular changes may have been related to respiratory changes, the effect of electrical stimulation of the septum on cardiovascular parameters was studied in 12 animals before and after the administration of tubocurarine (75 μg/kg iv). In this series of animals the characteristic arterial pressure responses described for the medial and lateral septum in animals under the two anesthetics were not changed by the administration of d-tubocurarine (Table 2).

DISCUSSION

The effect on cardiovascular parameters of electrical stimulation of histologically confirmed sites in the lateral septum in rats under chloralose anesthesia confirms previous reports of cardiovascular responses to septal stimulation (2,
have not been described before. The possibility that the ob-

served changes in arterial pressure were secondary to respi-

torical stimulation of the medial septum in animals under the

5, 6). In addition, our experiments demonstrate that elec-

trical stimulation of the medial septum in animals under the

same anesthetic elicits the opposite arterial pressure re-

sponse. The hypotensive response during stimulation of the

lateral septum and the hypertensive response during stimula-

tion of the medial septum are reproducible events and have not been described before. The possibility that the ob-

served changes in arterial pressure were secondary to respir-

atory alterations is remote because of the short latency, the

reproducibility of the two opposite cardiovascular responses

in the presence of consistent respiratory alterations (see

Table 1), and the persistence of the cardiovascular responses

after respiratory paralysis (see Table 2). It can also be ex-

cluded that the arterial pressure responses were secondary to

muscular activity because these responses were still present

after administration of tubocurarine. In addition, it may be

concluded that the hypertensive response was undoubtedly
due to a neural event and not to the release of adrenal cate-

cholamines as the response had a latency of approximately 3

sec, a delay much shorter than that observed between cen-

tral stimulation and cardiovascular changes brought about

by the liberation of adrenal catecholamines (17).

The observation of changes in arterial pressure in opposite
directions during stimulation of the two locations in the

septum and the finding of a hypertensive-hypotensive re-

sponse in animals under chloralose during stimulation of

sites at the border between medial and lateral septum

strongly suggests the possibility of the existence within the

septum of two well-defined functional areas affecting the

vasomotor system in two distinct ways. However, the present

state of knowledge does not permit an explanation of the

results in terms of different connections of the medial and

lateral septum to different hypothalamic regions. In fact, al-

though it has been shown that the stimulation of the fornix

and stria terminalis, which receive fibers from the septum,

elicit differential effects on certain functions (16, 22), it is

unlikely that these two pathways receive inputs exclusively

from the medial septum or the lateral septum. In addition,
it is known that the medial forebrain bundle, the other main

pathway from the septum to the hypothalamus, originates

in both medial and lateral septum (10, 20).

Our finding that the optimum frequency and duration of

stimulation to elicit the hypotensive response during stimu-

lation of the lateral septum were 80 Hz and 2 msec does not

agree with previous reports (6). The origin of this discrep-

ancy cannot be readily explained. It must, however, be

pointed out that the doses of α-chloralose used in these ex-

periments were higher than those used by previous workers

(15 mg/100 g body wt vs. 8 mg/100 g), as in our experi-

ence the lower dose did not ensure adequate surgical anes-

thesia. In addition, it must be noted that the same parame-

ters, i.e., 2 msec and 80 Hz, were found to elicit optimal

hypertensive responses during stimulation of the medial

septum, which suggests a similar degree of responsiveness

throughout the septum.

The observation that in animals under urethan anesthesia

the arterial pressure responses to septal stimulation were in

the opposite direction to those obtained in animals under

chloralose was an unexpected finding; this clearly points to

the difficulties of interpretation of experiments on the cen-

tral neural control of the cardiovascular system when differ-

ent anesthetics are used. These responses in the animals

under urethan were easily reproducible and, like those ob-

served in animals under chloralose, were not affected by the

administration of tubocurarine, did not appear to depend on

respiratory changes, showed a distinct functional localiza-

tion in the two parts of the septum, and were optimally

elicted by stimuli of 2 msec at 80 Hz.

In attempting to explain the opposite responses to elec-
trical stimulation of the septum in animals under the two anesthetics used in this study, it is worth noting the difference in control mean arterial pressure in the two series of animals (Table 1); animals under chloralose had a higher level of mean arterial pressure than animals under urethan. This suggests the presence of a higher level of sympathetic activity in chloralosed animals. As no attempts have been made in these experiments to investigate the mechanisms responsible for the observed cardiovascular responses, no physiological explanation can be suggested regarding the functional role of the septum on the cardiovascular system of animals with different degrees of sympathetic tone. However, as it has been previously reported that electrical stimulation of the same central structure can elicit changes in heart rate in opposite directions in two different preparations (4), it seems reasonable to suggest that the septum may induce changes in cardiovascular parameters whose direction depends on the base-line setting of the cardiovascular system. This suggestion may point to a homeoeustatic role of the septum in the maintenance of arterial pressure and is given substance by the demonstration (15) that electrical stimulation of the septum has opposite effects on the discharge rates of hypothalamic neurons depending on the base-line discharge rate: when hypothalamic neurons were firing slowly, septal stimulation enhanced the discharge rate, and when they were firing at a faster rate, septal stimulation had an inhibitory effect.

A very interesting finding in the course of these experiments was the rhythmic oscillation of arterial pressure during the hypertensive response elicited by electrical stimulation of the lateral septum in animals under urethan. The remarkable consistency of the frequency of oscillation (24.6 ± 0.2) appeared to be independent of respiratory frequency and of the frequency and duration of the stimulating pulses. These results cannot be readily interpreted without further experiments, but suggest the existence in the septum of a generator of rhythmic discharges controlling the level of arterial pressure. The physiological significance of such a generator is obscure at the present time, but similar rhythmic generators have been described previously (7). With regard to the consistent changes in respiratory rate elicited by septal stimulation in both groups of animals under two different anesthetics, although it can be excluded that they were related to the observed cardiovascular changes, it must be concluded that the septum is capable of influencing the central control of the respiratory system. However, how this control is exercised and its physiological significance remain, at the moment, matters of speculation.

In summary, it has been shown that histologically localized stimulation of the medial and lateral septum elicits opposite arterial pressure responses in rats under chloralose. In addition, it has been shown that these two responses are reversed when stimulation is done in animals under urethan. The differences in the results clearly indicate the importance of the anesthetic used in the interpretation of experiments on the central control of the cardiovascular system and may be accounted for by the difference in the basal level of arterial pressure in the two preparations. Furthermore, the demonstration of a rhythmic oscillation of arterial pressure at a consistent frequency suggests the presence in the septum of a pattern generator influencing arterial pressure.

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