Table 1. Effect of compounds on the estrus cycle of the rat. Animals were given 20 μg of compounds subcutaneously each day for 28 days in experiment 1, and 50 μg (twice daily) in experiment 2 for 60 days. Controls received an equal volume of vehicle. Smears were taken daily, after vaginal opening, and examined microscopically for incidence of estrus. Results are expressed as the percentage of positive estrus smears encountered in each group. In experiment 1 a total of 500 smears were examined, 100 from each group. In experiment 2, 600 smears were examined representing 60 cycles in the control group.

Substance tested	Positive smears (%)	
	Expt. 1	Expt. 2
None (Control)	43	47
N-Formyl-5-methoxytryptamine	35	
5-Hydroxytryptophol	40	
N-Acetyl-5-methoxytryptamine	30	
5-Methoxytryptophol	12	22

Table 2. Effect of compounds on the rat ovary. Compounds were administered subcutaneously at a dose of 20 μg per day for 28 days in experiment 1 and 50 μg twice daily for 60 days in experiment 2. Control animals were given equal volumes of vehicle.

Compounds	Ovary weight (mg) per 100 g body weight ± S. E.	
	Expt. 1	Expt. 2
None (control)	50.8± 1.8	55.5±4.2
5-Methoxytryptophol	35.3± 2.2*	41.6±4.2†
N-Acetyl-5-methoxytryptamine	51.2± 6.3	
N-Formyl-5-methoxytryptamine	46.1± 9.7	
5-Hydroxytryptophol	50.0±11.3	

* $p < .001$. † $p < .001$.

administered subcutaneously in a single daily dose of 20 μg dissolved in aqueous alcohol or aqueous propyleneglycol for 28 days. The animals in the control group received solvent alone.

No significant difference in the rate of increase in body weight or in spontaneous vaginal opening were noted. After vaginal opening, daily smears were taken and examined microscopically for estrus (Table 1). In the control group, positive smears were obtained in 43 percent of the total smears. In the melatonin-treated group the incidence of estrus was reduced to 30 percent—which is in agreement with the findings of Wurtman, Axelrod, and Chu (*4*). The group treated with 5-methoxytryptophol, however, showed a more dramatic decrease in incidence of estrus, only 12 percent of the total smears being positive. In fact, in three out of the five rats there was complete suppression of estrus. On the 28th day the animals were killed and the ovaries were weighed (see Table 2); ovarian weights in the group treated with 5-methoxytryptophol were significantly less than in the control or other treated groups.

In a second experiment 20 female Sprague-Dawley rats, all born on the same day, were divided into two groups of ten, and administration of 5-methoxytryptophol (50 μg) or vehicle twice daily subcutaneously was begun on the 23rd day of life. Spontaneous vaginal opening occurred on the 55 ± 0.6 day of life in the control group and on the 57 ± 1 day in the treated group. Daily vaginal smears were examined microscopically and the incidence of estrus in the treated group was significantly less than in the control group (Table 1). Two months after the beginning of the experiment, when the animals were 84 days old, they were killed and the organs were weighed. Ovarian weights in the treated group were significantly less than those in the control group (Table 2).

Therefore O-methylated indoles present in the pineal gland appear to reduce the incidence of estrus in rats, 5-methoxytryptophol being the most potent compound so far tested. The previous report on the effect of *N*-acetyl-5-methoxytryptamine (*4*) and the present finding of the effect of 5-methoxytryptophol in significantly reducing ovarian weight after daily administration of microgram quantities would support the hypothesis that methoxy indoles present in pineal are responsible for some of the antigonadotrophic effects of pineal extracts previously reported (*1, 3*).

WILLIAM M. MCISAAC
ROBERT G. TABORSKY
GORDON FARRELL

Cleveland Clinic and
Department of Physiology, Western University, Cleveland 6, Ohio

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Tonic Influence of Rostral Brain Structures on Pressure Regulatory Mechanisms in the Cat

Abstract. *Transection of vagi and carotid sinus nerves in anesthetized cats results in a rise of blood pressure and subsequent decerebration results in a fall. Decerebration alone results in a slight drop in blood pressure unchanged by subsequent nerve section. Rostral brain structures principally influence tonically brainstem mechanisms subserving baroreceptor reflex excitability rather than those maintaining normal blood pressure.*

It has generally been accepted that the brain structures lying above the pons do not participate in the maintenance of systemic blood pressure at "normal" levels since it has been repeatedly confirmed in animals (*1*) that the blood pressure remains unchanged with serial transections of the brain until transections are made in the upper or mid-pons.

In the course of a study on the cerebral neural regulation of carotid sinus baroreceptor reflexes made on bilaterally vagotomized cats with one carotid sinus nerve sectioned (*2*), we were therefore surprised to observe that transection of the brainstem anywhere between the superior colliculus and the optic chiasm, rostrally, and the pontomesencephalic border, caudally, invariably resulted in an immediate, significant, and sustained fall of the mean aortic blood pressure. Also, the reflex fall of blood pressure to stretch of the innervated carotid sinus was augmented. The pressor response to occlusion of the same carotid artery was inhibited and the heart rate was slowed. Since our animals, unlike those used in other studies, had both vagi and one carotid sinus nerve sectioned and hence had lost three of their four "buffer" nerves, it appeared that the drop in blood pressure was due to the difference in the preparations. If so, it would suggest that there was a tonic effect of telencephalon—basal ganglia or cortex—or thalamus on blood pressure regulatory mechanisms which was masked by intact buffer nerves. In order to test this hypothesis, two series of animals were compared in which both midcollicular decerebration and section of the "buffer nerves" were performed in different sequence.

The experiments were performed on 37 adult cats usually anesthetized with α-chloralose (60 mg per kilogram of

body weight) which was occasionally augmented with small doses of pentothal (5 mg/kg) during induction. Some cats were anesthetized with nembutal (40 mg/kg), and a few were decerebrated under ether.

External carotid blood pressure and aortic blood pressure were recorded through cannulas attached to a Stathem strain gauge and led to channels of a Grass polygraph. Heart rate and respiration were also recorded. The vagi were sectioned in the neck and the carotid sinus nerves near their junction with the glossopharyngeal nerves. Decerebration was performed under direct vision by removing the occipital lobe and by partially sectioning the brainstem at the midcollicular level with a spatula and completing the separation by suction. This method achieved a sharp anatomical demarcation with minimal bleeding. Blood pressure measurements, always made with the animals supported in the prone position, were taken at least 30 minutes after decerebration or nerve section. The levels of transections were verified histologically.

The results are shown in Fig. 1. The solid line represents animals which had the buffer nerves sectioned (*S*) before decerebration (*D*). The broken line represents animals which were decerebrated before sectioning of the buffer nerves. It was observed that in the intact animal decerebration (broken line, *D*) resulted in a small drop of the mean blood pressure from an average of 119 to 103 mm-Hg, a fall of 14 percent which was not statistically significant. If then the buffer nerves were sectioned (broken line, *S*) there was no change of the blood pressure of the group and in some animals a slight fall of the blood pressure was seen. In contrast, section of the buffer nerves in the intact animal (solid line, *S*) resulted in a prompt and significant ($p < .001$) rise in the mean blood pressure from an average 118 to 150 mm-Hg, or an increase to 27 percent above the control. Decerebration in these animals (solid line, *D*) resulted in a significant ($p < .001$) fall of the mean pressure from a new pooled average of 143 to 100 mm-Hg, a fall of 30 percent. The break in the solid line at (*D*) results from comparing two different groups of animals. There is little difference in the mean blood pressure of the two groups before as well as after the two surgical interventions. The pattern of response was identical for sections made at any plane within the described region. Differences in anesthesia or degree of rigidity after decerebration did not change this pattern of response.

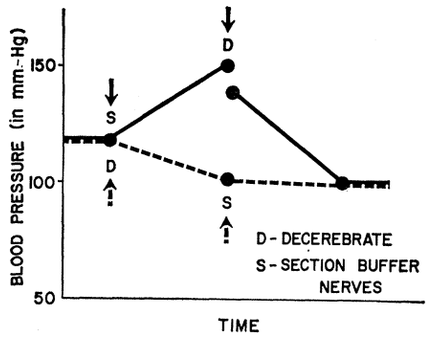

Fig. 1. Schematic representation of changes in blood pressure after decerebration and section of buffer nerves in alternate sequence. Solid line represents animals which had the buffer nerves sectioned (*S*) before decerebration (*D*). Broken line represents animals which were decerebrated before sectioning of buffer nerves. The average of mean blood pressure is shown for grouped animals. The groups were slightly different for decerebration after section.

Therefore, in the absence of both vagi and one or both carotid sinus nerves decerebration produces a fall of blood pressure which on the average returns the blood pressure to (or slightly below) that found before section of the buffer nerves. Structures above the hypothalamus thus appear to exert a tonic influence on some part of the blood pressure regulatory mechanism in pontomedullary regions which is concealed in the decerebrated animal when the buffer nerves are intact.

It is evident, however, that these observations cannot be explained on the basis that the fall of blood pressure which might result from withdrawal of tonic outflow from forebrain or thalamus by decerebration is masked in the otherwise intact animal by compensatory baroreceptor reflexes. If such were the case, sectioning of the nerves in the decerebrate animal should result in a marked fall of the blood pressure, an effect which was not seen. Thus it appears that these rostral brain areas do not on the whole exert any significant tonic effects on those vasomotor neurons of the lower brainstem whose integrity has been demonstrated repeatedly (*1*) to be necessary for the maintenance of normal blood pressure.

The results suggest that as yet unidentified telencephalic or thalamic structures maintain the responsivity of neurons which participate in determining the excitability of baroreceptor reflexes. The absence or reduction of the rise of blood pressure after transection of the buffer nerves in the decerebrate animal can be interpreted as resulting from withdrawal of tonic excitation from neurons modulating the pressor reflex to reduction of baroreceptor afferent activity. This view is supported by the observation that the reflex pressor response to brief carotid occlusion in the decerebrate animal is inhibited (*2*). Similarly, the fall in blood pressure (to or near that of controls) that follows decerebration after the buffer nerve has been sectioned can be explained as a result of an interruption of a tonic descending excitatory outflow to neurons taking part in the reflex pressor response but not to those necessary for the maintenance of normal blood pressure.

As yet unidentified structures in either telencephalon or thalamus, which hitherto have been considered of no consequence in the tonic regulation of blood pressure, play a role in its control. Also there is evidence to support a view (*3*) that the neuronal substrate of the baroreceptor reflexes is in great part distinct from the tonic vasomotor neurons of the lower brainstem. Our study indicates that these two neuronal groups can be differentiated by having different afferent inputs, the neurons modulating baroreceptor reflex excitability receiving afferents from areas above the hypothalamus which are not shared by vasomotor neurons. The same is probably true for some cerebellar projections since it has been demonstrated that baroreceptor reflex excitability may be altered by ablation (*2*) or stimulation (*4*) of this organ without changing the blood pressure. Thus, at least part of the regulation of cardiovascular performance by higher brain regions may be mediated indirectly through baroreceptor reflex mechanisms.

DONALD J. REIS*
MICHEL CUÉNOD†
Laboratory of Neurophysiology, National Institute of Mental Health, Bethesda, Maryland

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* Present address: Department of Neurology, Cornell University Medical College, New York 10021.
† Present address: Department of Pharmacology, New York State Psychiatric Institute, Columbia University, New York.

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