higher integral and fractional order may also be distinguished.

The overall trend of the curve is positive, corresponding to the fact that, in general, an increased excitation frequency, or a decreased inhibition frequency, will result in an increased firing rate of the cell. With regularly spaced input (solid curve in Fig. 1), however, some portions of the curve have a slope opposed to the overall trend. These portions give rise to the "paradoxical" effect: namely, that an increased frequency of inhibition, or a decreased frequency of excitation, will cause an increase in the firing rate of the "inhibited" or "less excited" cell.

The "paradoxical" regions for inhibited cells correspond to the stability zones; within each such region, the firing rate is proportional to the inhibition rate, with a different constant of proportionality for each zone. The corresponding "paradoxical" effect for excitation takes place just outside the stability zones, where a small increase in EPSP's frequency can cause a drastic decrease in firing rate. The change is not proportional, however, and the pattern of EPSP's and spikes is constantly shifting, as contrasted with the stable temporal patterns produced by "paradoxical" frequencies of IPSP's.

With "random" Poisson arrivals, a relatively smooth response curve is observed. Additional curves were computed in which the intervals between the postsynaptic potentials were normally distributed; with increasing variance in the arrival interval, the stability zones become narrower and less clearly delineated (*2*).

In pacemaker cells in the isolated abdominal ganglion of *Aplysia,* the observed input often consists of regularly spaced IPSP's, evoked (presumably) by another pacemaker cell. A constant latency between spike and IPSP is frequently observed; if disrupted, for example by stimulation of a nerve, the constant latency is eventually reestablished (Fig. 1*b*). Various stable sequences of interspike intervals are found, corresponding to various stability zones (Fig. 1, *b–d*); unstable "interzonal" sequences are also found. Where the delay function was known, the order of the zone and the input and output frequencies conformed to the theoretical predictions.

The stretch receptor of the crayfish (*Procambarus clarkii*) operates as a pacemaker when submitted to moderate stretch (*4*). A single inhibitory fiber makes a direct monosynaptic contact with the neuron; this fiber was subjected to electrical stimulation at regular intervals. The curve of the mean output frequency plotted against the mean input frequency (Fig. 4) is essentially similar to that of the simulated pacemaker (Fig. 3). Some of the low-frequency zones are visible, but the higher-order ones are absent, because the IPSP was of sufficient magnitude to cause total inhibition at frequencies beyond the primary stability zone. The "paradoxical" effect of regularly spaced inhibition is apparent.

The mechanism described determines stable patterns in which, over a clearly defined frequency range, the output discharge is locked in phase and frequency with the input; these phase relationships are restored spontaneously after interruption of the input. This is accomplished without feedback, that is, without closed-loop or reciprocal interaction (*5*). A mathematical term related to the slope of the delay function plays a role analogous to that of a feedback signal and accounts for the self-stabilizing properties. Many physiological possibilities suggest themselves; we may mention the following: (i) Such systems are capable of maintaining stable phase relationships among discharging units, such as would be required of antagonistic and synergistic motor units responsible for coordinated movements. (ii) Since small changes in rate of synaptic input or in input variance can markedly alter the output pattern, highly selective filtering or switching becomes possible in these networks, particularly if coupled with cells that are pattern sensitive, as have been previously described (*6*).

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5-Methoxytryptophol: Effect on Estrus and Ovarian Weight

Abstract. *Daily injection of 5-methoxytryptophol in microgram quantities in rats decreased the incidence of estrus and reduced ovarian weight in maturing animals.*

The administration of extracts from the pineal gland of rats caused a decrease in ovarian weight and provided histologic evidence of retarded ovarian maturation (*1, 2*). The reduction in incidence of spontaneous estrus and antagonism of light-induced estrus in rats has been reported (*3*). Wurtman, Axelrod, and Chu (*4*) have shown that some of the effects of the pineal gland on gonad function might be mediated by melatonin. Melatonin (5-methoxy-*N*-acetyltryptamine) is localized in the pineal gland (*5*) and is the product of hydroxyindole-O-methyl transferase (*6*) acting on the substrate *N*-acetylserotonin, a metabolite of serotonin (*7*). There is evidence that the pineal gland also contains other indolic compounds including 5-hydroxytryptophol and 5-methoxytryptophol (*8*). Hydroxyindole-O-methyl transferase, present only in pineal tissue (*6*), converts 5-hydroxytryptophol to 5-methoxytryptophol (*8*).

We have studied compounds known or thought to be present in the pineal gland in relation to the incidence of estrus and ovarian weight in rats. Since *N*-formyl-5-methoxytryptamine is indistinguishable by chromatographic and spectroscopic examinations from melatonin, it was also tested.

In the first experiment, 25 immature 27-day-old female Sprague-Dawley rats (average weight 60 grams) were divided at random into five groups of five each. The compounds tested, *N*-acetyl-5-methoxytryptamine, *N*-formyl-5-methoxytryptamine, 5-hydroxytryptophol, and 5-methoxytryptophol, were

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*).

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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