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9. This work was performed while one of us (J.C.J.) was a guest at the Poulter Laboratories. We thank Thomas C. Poulter, director of the Poulter Laboratories, for his advice and support. We also thank E. Anders, University of Chicago, for convincing us that the transition was feasible, and B. Alder of Lawrence Radiation Laboratory for some of his unpublished experimental results.


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## Role for Ganglionic Norepinephrine in Sympathetic Synaptic Transmission

*Abstract.* Transmission of nerve impulses in superior cervical sympathetic ganglia of cats and rabbits is markedly enhanced after reserpine-induced depletion of ganglionic norepinephrine. Transmission is also enhanced by administration of adrenergic blocking agents. In contrast, reserpine-induced release of ganglionic norepinephrine in animals pretreated with a monoamine oxidase inhibitor results in a pronounced depression of ganglionic transmission, which lasts until the ganglionic norepinephrine disappears. These results support the concept that norepinephrine in ganglia modulates the action of acetylcholine.

The fact that stimulation of preganglionic sympathetic nerves releases catecholamines from ganglia (*1*), together with the recent discovery that sympathetic ganglia contain considerable amounts of norepinephrine (*2*), prompts speculation on the role of the amine in the regulation of synaptic transmission. In this regard, Marrazzi and others have demonstrated that the injection of epinephrine and norepinephrine causes inhibition of ganglionic transmission (*3*). However, conclusions concerning the physiological role of a naturally occurring amine are questionable when they are based on studies of the injected substance. For example, the injection of histamine and even serotonin, a substance absent from sympathetic ganglia, also modifies ganglionic transmission (*4*).

We decided that a more direct approach to studying the role of norepinephrine in ganglia would be to compare synaptic transmission before and after depletion of the amine. The present report describes experiments which implicate ganglionic norepinephrine as a modulator of transmission in sympathetic ganglia. In these experiments changes in synaptic transmission were measured in cats and rabbits under chloralose anesthesia by applying graded electrical stimuli to the superior cervical sympathetic nerve and recording the electrical activity postganglionically before and after the intravenous injection of reserpine in various doses. The norepinephrine content of the superior cervical sympathetic ganglion was determined by a specific fluorimetric procedure which measures total (bound plus free) catecholamine and detects as little as 0.040 $\mu$g of amine (*5*).

Reserpine in doses up to 0.2 mg/kg had no effect on ganglionic transmission; a definite increase was produced with 0.6 mg/kg, and maximal enhancement with 1.25 mg/kg. In control animals not given reserpine, the evoked potential remained relatively constant over a period of 20 hours. As shown in Table 1, facilitation of synaptic transmission was associated with a reduction in the level of amine of more than 90 percent.

Table 1. Norepinephrine concentration in cat superior cervical ganglia 4 hours after administration of various doses of reserpine. The drug, dissolved in water as the lyophilized phosphate salt, was given intraperitoneally, and the animals were killed 4 hours later. Norepinephrine concentrations are mean values, and numbers in parentheses indicate the number of animals.

| Dose of reserpine (mg/kg) | Norepinephrine content ($\mu$g/g) |
|---|---|
| | 7.1 (16) |
| 0.005 | 6.9 (4) |
| 0.025 | 5.0 (8) |
| 0.050 | 3.0 (6) |
| 0.200 | 1.0 (8) |
| 0.600 | $<$1.0 (6) |

Figure 1 (typical of 12 experiments) shows the postganglionic response evoked by submaximal and supramaximal stimuli at various times after administration of reserpine (2.5 mg/kg). After a latent period of about 4 hours the evoked potential was definitely higher than the control value; it continued to increase and was maximal in about 7 hours. The enhancement of the potential persisted throughout the 12 hours of the experiment. In

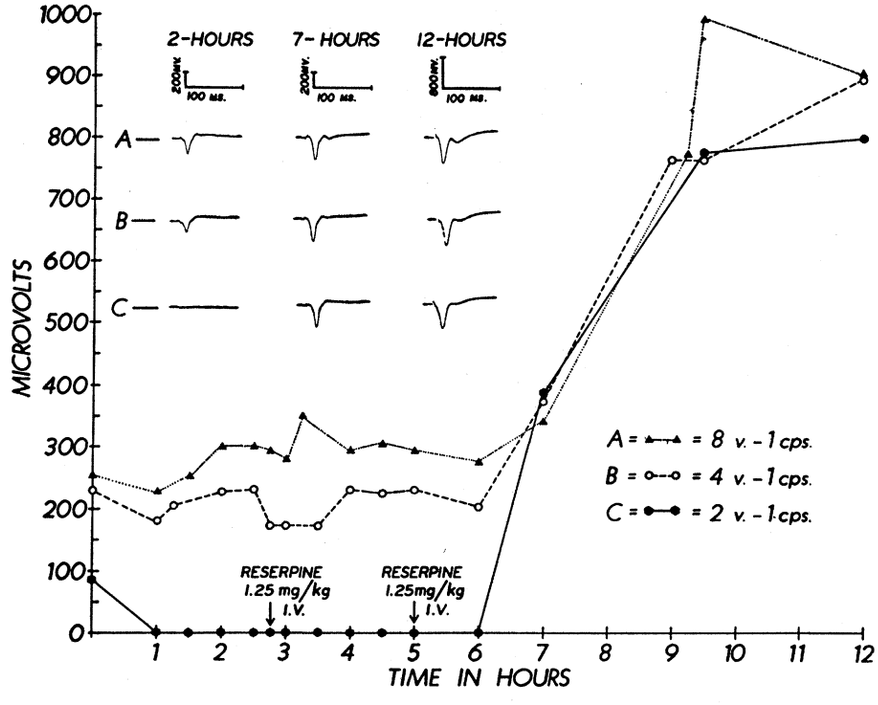


Fig. 1. Effect of reserpine on amplitude of postganglionic potential in response to graded electrical stimuli applied preganglionically to superior sympathetic ganglion. Stainless steel electrode pairs were used. Subthreshold (2 volts, 1 cy/sec, 0.01 msec) and supramaximal (8 volts, 1 cy/sec, 0.01 msec) stimuli were applied in control period. Reserpine (2.5 mg/kg) was administered in divided doses at the indicated times. Records of 10 potentials, 1 second apart, measured at 2, 7, and 12 hours (upper left of the figure), indicate the reproducibility of the response. Note the reduction in amplification required to record the 12-hour response.

some experiments stimuli which produced no effect in the control period now evoked a potential equal to the greatest response produced by supramaximal stimuli. In the rabbit, transmission of impulses across the superior cervical sympathetic ganglion was also facilitated by doses of reserpine that depleted ganglionic norepinephrine.

Experiments with cats given adrenergic blocking agents provided additional evidence of a role for norepinephrine in ganglionic transmission. Within 20 minutes after the intravenous injection of 1 mg of ergotamine per kilogram, the potential evoked by supramaximal stimuli was facilitated by 200 percent or more for a period of at least 1 hour. Similar effects were produced with 20 mg of dibenamine per kilogram. Preliminary results have shown that ganglion transmission is also facilitated by bretylium, a hypotensive drug that prevents the physiologic release of norepinephrine from sympathetic nerve endings (*6*).

Since transmission was enhanced in ganglia devoid of norepinephrine, the question could now be raised whether transmission would be inhibited in ganglia containing an accumulation of the free amine at the sites of release. A high level of free norepinephrine in ganglia was produced by treatment of cats with MO 911 (*7*), a potent monoamine oxidase inhibitor (*8*), and then by releasing the amine from storage by means of reserpine (1.25 mg/kg). As a result of blocking monoamine oxidase, the disappearance of the norepinephrine released in ganglia by reserpine was much slower than in animals given reserpine alone. Thus 1 hour after reserpine administration, the level of norepinephrine in the ganglia of cats given both the monoamine oxidase inhibitor and reserpine was 2.7 $\mu$g/g (mean of four ganglia) compared with traces of amine in ganglia of animals given reserpine alone. Within 15 minutes after administration of the alkaloid, the potential evoked by submaximal stimuli was almost completely blocked; even the potential evoked by supramaximal stimuli was markedly reduced. In 2 to 3 hours, when the free norepinephrine had finally diffused away, facilitation of the evoked potential was again observed.

The data presented here support the concept that norepinephrine as well as acetylcholine is implicated in transmission phenomena in sympathetic synapses. Cholinergic ganglionic transmission may be considered to effect the release of norepinephrine which in some unknown manner counteracts the effect of acetylcholine in the postsynaptic membrane. The reciprocal relationship between acetylcholine and norepinephrine in sympathetic ganglia might be important in buffering large fluctuations in central sympathetic output. These results bring up the possibility that in the brain there is also a reciprocal relationship between the chemical transmitter and norepinephrine or serotonin, the monoamines serving as modulators of synaptic transmission rather than as transmitting agents.

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## Ionium-Thorium Chronology of Deep-Sea Sediments of the Western North Pacific Ocean

*Abstract.* The rate of deposition of deep-sea deposits collected at the depths of 6215 to 8450 m in the western part of the North Pacific Ocean was estimated by means of the ionium/thorium ratio. The ratio was determined by an alpha-ray spectrometer. Results showed the rate of 0.5 to 0.8 mm/$10^3$ yr for the upper 10-cm layer below the sea bottom.

Pelagic sediments provide important records of geological processes in the ocean in the past. To estimate the rate of sedimentation, distribution of chemical elements with radioactivity has been extensively studied. The ionium-thorium geochronology (*1–3*) is one of the processes which is based on the assumption of simultaneous removal and deposition of two isotopes of thorium, ionium ($Th^{230}$, a member of the $U^{238}$ series; $T_{\frac{1}{2}}$, 80,000 yr) and thorium ($Th^{232}$; $T_{\frac{1}{2}}$, $1.4 \times 10^{10}$ yr), from sea water. Another assumption of this method is that the Io/Th ratio remains constant in a given water mass over the period under consideration. The contribution of thorium and uranium from detrital minerals of continental or volcanic origin must be negligible or can be accounted for.

Recently, Goldberg and Koide (*2*) developed the alpha-ray spectrometric method for determination of ionium and thorium in deep-sea deposits. They have found an exponential decrease in the Io/Th ratio with the depth of burial which indicates that the ionium may not be redistributed after deposition. Rona, Akers, and Parker (*3*) also applied the same method to the age determination of North Atlantic deposits. In our laboratory, attempts have been made to obtain ages, by means of the Io/Th ratio, of deep-sea sediments of the western North Pacific collected at various depths from aboard the research vessel, M.S. *Ryofu-maru.*

One to two grams of dried sediments were subjected to leaching with a hot solution of a mixture of hydrochloric and perchloric acid. The residue was separated by centrifuge, and leaching was repeated. The solution was nearly dried up on a sand bath and dissolved again in dilute hydrochloric acid from which silica was removed by filtration. The acidity of the filtrate was adjusted to a 3*f* solution of hydrochloric acid.

Thorium isotopes were isolated from the filtrate with a cation-exchanging resin. The thorium isotopes have a strong tendency to adsorb selectively on the cation exchanger, while there is little adsorption of aluminum, iron, and other cations in the hydrochloric acid media of high concentration. The cation exchanger of HR form, Amberlite IR-120 of 100 to 200 mesh, was used in a column 4 mm in diameter and 5 cm long. A solution was passed through the column at a flow rate of approximately 1 ml/min. The column of the resin in which thorium isotopes were adsorbed was rinsed with the hydrochloric acid solution (4*f*) and water. Thorium isotopes were subsequently eluted with 0.5*M* oxalic acid. The thorium contained in the effluent was plated on a platinum disk 4 cm in diameter; this was followed by ignition to remove oxalic acid. Another thorium isotope, $Th^{234}$ ($UX_1$), which was prepared by the method of Cowan (*4*), was used as a radioactive tracer to determine the chemical yield. The recovery of the thorium isotopes was checked each time with the activity of beta rays of $Th^{234}$. The results of tracer experiments gave a yield ranging from 70 to 97 percent.

The intensities of the alpha rays of $Th^{230}$ and $Th^{232}$ plated on the platinum disk were measured with an alpha-ray spectrometer, which consists of a Frisch grid-ionization chamber (Tracerlab), combined with a high-gain amplifier and a pulse-height analyzer. Since alpha-particles of Io and Th have dominant