infect the substantia nigra makes it a potential animal model for postencephalitic parkinsonism. In light of the experience with encephalitis lethargica, in which parkinsonian symptoms progress for months to years after the initial infection, the relation of a previous virus infection to the development of idiopathic Parkinson's disease has long been considered (*18*). However, most Parkinson's disease patients have no history of encephalitis, and there is no evidence for infection by any of several studied viruses (*18, 19*). Although the tropism of MHV-A59 for the basal ganglia is reminiscent of encephalitis lethargica, there are differences in pathology between these two encephalitides. Neither demyelination nor cellular vacuolation are seen in encephalitis lethargica, while neurofibrillary tangles, commonly seen in postencephalitic parkinsonism, are not seen in MHV-A59 encephalitis. The antigen-dense, necrotizing lesions in MHV-A59 infection encompass a variable amount of the subthalamic nucleus and only the more rostral portion of the nigra. Von Economo's disease destroyed most of the nigra, although, like this experimental encephalitis, it affected other regions of the brain as well (*20*). A possible role for coronaviruses in the pathogenesis of postencephalitic parkinsonism or Parkinson's disease remains a subject for future investigation, as does the mechanism through which this coronavirus consistently and selectively infects this clinically important region of the brain.

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Depolarization and Muscarinic Excitation Induced in a Sympathetic Ganglion by Vasoactive Intestinal Polypeptide

Abstract. *The effects of vasoactive intestinal polypeptide (VIP) in the superior cervical ganglion of the cat were studied in vitro and in vivo with sucrose gap and multiunit recording, respectively. At a dose of 0.03 to 0.12 nanomole, VIP produced a dose-dependent, prolonged (3 to 15 minutes) depolarization of the ganglion and enhanced the ganglionic depolarization elicited by the muscarinic agonist acetyl-β-methylcholine. At a dose of 1.8 to 10 nanomoles, the peptide enhanced and prolonged the postganglionic discharge elicited by acetyl-β-methylcholine, enhanced muscarinic transmission in ganglia treated with an anticholinesterase agent, and enhanced the late muscarinic discharge elicited by acetylcholine. VIP did not affect the early nicotinic discharge elicited by acetylcholine or by electrical stimulation of the preganglionic nerve. It is concluded that VIP has a selective facilitatory action on muscarinic excitatory mechanisms in the superior cervical ganglion of the cat.*

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Recent studies (*1–3*) have focused attention on the synaptic interactions between vasoactive intestinal polypeptide (VIP) and acetylcholine (ACh). In the submandibular gland, VIP and ACh coexist in the parasympathetic postganglionic nerves and are released during nerve stimulation (*1*). VIP mediates neurally evoked vasodilation in the gland and also facilitates ACh-induced glandular secretion (*1, 2*). Radioligand receptor binding studies suggest that VIP enhances the secretory effect of ACh by increasing the affinity of ACh for muscarinic receptors on the gland cells (*3*). Thus VIP seems to function as a neuromodulator and a transmitter at certain cholinergic neuroeffector junctions.

A similar facilitatory effect of VIP on neuronal muscarinic mechanisms in vesical parasympathetic ganglia of the cat was shown by recent studies in our laboratory (*4*). Exogenous VIP enhanced muscarinic transmission and the ganglionic excitatory responses to muscarinic agonists but did not alter nicotinic transmission or the responses to nicotinic agonists. These observations suggested that VIP must have a very selective postsynaptic effect to alter the interaction of ACh with muscarinic receptors or to alter the transduction mechanisms leading to muscarinic depolarization and ganglion cell firing. Other investigators have reported that VIP also increases adenosine 3′,5′-monophosphate (cyclic AMP) concentrations (*5*) and tyrosine hydroxylase activity in autonomic ganglion cells (*6*). These observations, coupled with the immunohistochemical demonstration of VIP axons and varicosities in autonomic ganglia (*7*), indicate that VIP may be a transmitter or a modulator of cholinergic transmission at ganglionic synapses.

The effects of VIP were examined in eight ganglion preparations in vitro and ten preparations in vivo. For the in vitro experiments, superior cervical ganglia were removed from barbiturate-anesthe-

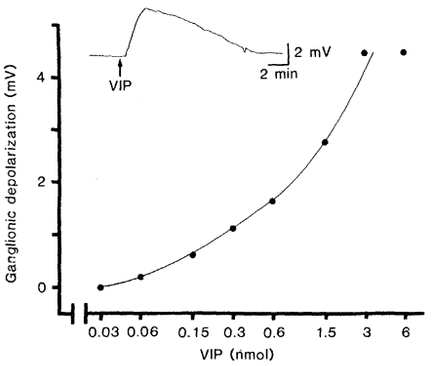

Fig. 1. Dose-response curve for VIP-evoked depolarization of the cat superior cervical ganglion in vitro. The curve represents the average of responses from three ganglia. Depolarization was recorded with the sucrose gap technique. The threshold dose is approximately 0.06 nmol and the maximum effect occurs at 3 nmol. Inset: depolarization evoked by a VIP dose of 6 nmol.

tized cats and placed in a 1-ml sucrose gap chamber (*8*) perfused with oxygenated (95 percent O_2 and 5 percent CO_2) Krebs-Ringer solution at a flow rate of 0.4 to 0.6 ml/min and a temperature of 20° to 24°C. Ganglionic potentials were recorded with a direct-coupled preamplifier (*8*). Drugs were administered by injecting 0.05 ml of solution into the perfusion fluid. Injection of saline or Krebs-Ringer did not alter the baseline ganglion potentials. The in vivo experiments were conducted in dial urethane–anesthetized cats. The superior cervical ganglia were exposed and the cervical sympathetic trunks were cut. Postganglionic nerves were isolated for monophasic recording and drugs were administered by close intra-arterial injection (0.1 ml) into the common carotid artery. Postganglionic discharges were elicited by electrical stimulation of preganglionic nerves or by injection of nicotinic or muscarinic agonists.

Administration of VIP to the superior cervical ganglion in vitro produced a delayed-onset (30 to 90 seconds), prolonged (3 to 15 minutes) ganglionic depolarization that was graded in amplitude over a range of doses (Fig. 1). Detectable depolarizations (100 to 200 μV) were elicited by doses of 0.03 to 0.12 nmol and maximal responses (3 to 5 mV in seven experiments) by 3 to 16 nmol. The effects of VIP were reproducible when the peptide was administered at 15- to 30-minute intervals. In these preparations the administration of ACh (11 to 30 nmol) or the muscarinic agonist acetyl-β-methylcholine (MCH; 0.5 to 2.8 μmol) elicited depolarizations of 3 to 7 mV. The responses to ACh occurred with a more rapid onset (10 to 30 seconds) than those to MCH or VIP (30 to 90 seconds). The depolarization elicited by VIP was not blocked by atropine (0.01 μmol), which abolished the response to MCH, or by hexamethonium (20 to 80 μmol) or *d*-tubocurarine (2 to 10 μmol), which blocked the depolarization produced by ACh.

When administered before ACh, VIP (5 to 20 nmol) did not alter the magnitude of the nicotinic depolarizing responses of this agonist; however, VIP markedly enhanced the muscarinic ganglionic depolarization produced by MCH (Fig. 2). This effect of VIP could be elicited by doses (0.03 to 0.15 nmol) that produced minimal direct ganglionic depolarization, although larger doses (0.3 to 2 nmol) that directly depolarized the ganglion produced a greater facilitation of the response to MCH. The facilitatory effect of VIP persisted for 10 to 15 minutes and consisted of an increase in the amplitude and duration of the muscarinic response. The facilitated response to MCH was not blocked by hexamethonium or *d*-tubocurarine but was completely and reversibly blocked by atropine (15 to 60 nmol) (Fig. 2).

The selective facilitatory effects of VIP on ganglionic muscarinic responses in vitro were also evident in vivo. The intra-arterial injection of VIP (1.8 to 10 nmol) 1 to 15 minutes before injection of MCH (50 to 150 nmol) markedly enhanced the postganglionic discharge elicited by the latter (Fig. 2B). VIP also enhanced the muscarinic late discharge elicited by ACh but not the nicotinic

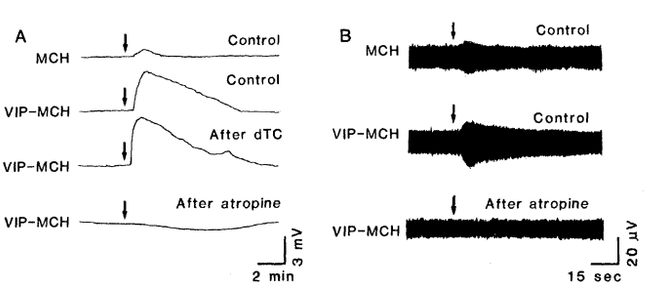

Fig. 2. Effect of VIP on the ganglionic response to MCH in vitro (A) and in vivo (B). (A) Sucrose gap recording showing that VIP in a dose (0.03 nmol) that did not elicit ganglionic depolarization enhanced the depolarization caused by MCH (2 μmol). This effect was not blocked by *d*-tubocurarine (dTC) (10 μmol) but was abolished by atropine (0.01 μmol). (B) VIP (5 nmol) facilitated the discharge elicited by MCH (150 nmol). This effect was abolished by atropine (0.01 nmol).

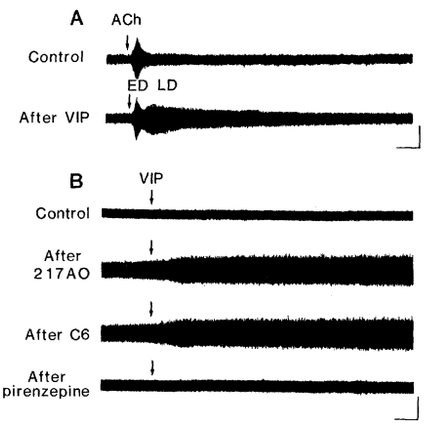

Fig. 3. Effect of VIP on ACh discharge in a sympathetic ganglion in vivo. While the early discharge (ED) was unchanged, the late discharge (LD) in response to ACh (1 μmol) was markedly enhanced. (B) Effect of VIP on muscarinic transmission. VIP did not elicit a discharge in untreated ganglia (control) but caused a marked discharge in ganglia treated with 217AO (100 nmol). This discharge was unaffected by hexamethonium (C_6) (20 μmol) but was completely abolished by pirenzepine (10 nmol).

early discharge (Fig. 3). Atropine blocked the firing elicited by MCH and the late discharge elicited by ACh (Fig. 2B).

Intra-arterial VIP (0.03 to 30 nmol) did not alter the amplitude of the postganglionic action potentials elicited by electrical stimulation of the preganglionic nerves. In addition, even large doses (10 nmol) were ineffective in eliciting postganglionic firing in the quiescent ganglion. However, VIP at 1.6 to 6 nmol elicited postganglionic firing or enhanced ongoing low-amplitude asynchronous firing in ganglia treated with an irreversible anticholinesterase agent, 217AO (30 to 150 nmol, intra-arterially) (Fig. 3B). The latter drug interferes with the metabolism of ACh in the ganglia, leading to the accumulation of spontaneously released transmitter and activation of postsynaptic muscarinic receptors (*9*). The 217AO-induced discharge can be viewed as a type of muscarinic ganglionic transmission. The VIP-induced discharge in 217AO-treated ganglia was not affected by hexamethonium in a dose that blocked nicotinic transmission but was blocked by atropine (2 to 15 nmol, intra-arterially) or by the selective M1 muscarinic antagonist pirenzepine (2 to 15 nmol) (*10*). The facilitatory effect of VIP on 217AO-induced firing occurred with doses from 0.5 to 3 nmol and persisted for 5 to 10 minutes depending on the dose.

These and other recent findings (*5*, *6*) indicate that VIP in nanomolar concentrations can elicit a variety of effects in

the superior cervical ganglia of the cat and rat. These effects include ganglionic depolarization, increased cyclic AMP, increased tyrosine hydroxylase activity, and selective enhancement of muscarinic excitatory responses without altering nicotinic transmission or the response to nicotinic agonists. A similar selective enhancement by VIP of muscarinic slow excitatory postsynaptic potentials (EPSP's) was recently described in the guinea pig inferior mesenteric ganglion (*11*). It is tempting to speculate that some of these responses are interrelated. For example, other agents, such as dopamine and isoproterenol, which increase cyclic AMP in the superior cervical ganglion of some species (rat, guinea pig, and cow) but not others (cat) (*12*), also enhance muscarinic slow EPSP's and enhance the ganglionic excitatory effects of muscarinic agonists (*13*). Exogenous cyclic AMP produces a similar facilitation of muscarinic slow EPSP's (*14*). Increased cyclic AMP therefore may contribute to the VIP-induced facilitation of muscarinic transmission in autonomic ganglia.

Cyclic AMP may also be involved in the VIP-induced depolarization of ganglion cells, since cyclic AMP applied intracellularly or extracellularly depolarized amphibian and mammalian sympathetic ganglion cells (*15*). Furthermore, in AH-2–type neurons in the guinea pig myenteric plexus, cyclic AMP or agents that increase cyclic AMP also produced membrane depolarization and other changes in neuronal electrophysiological properties during slow EPSP's (*16*). Exogenous VIP produces similar effects (*17*). Cyclic AMP has also been implicated in the VIP-induced phosphorylation and activation of tyrosine hydroxylase in the rat superior cervical ganglion (*18*). Thus, many of the effects of VIP on peripheral ganglia may be related to stimulation of adenylate cyclase.

The nature of the link between increased cyclic AMP and enhancement of muscarinic transmission is not known. Membrane depolarization by VIP would be expected to increase ganglion cell excitability and thereby facilitate the postganglionic firing elicited by various excitatory agents. While this effect could contribute to the VIP-induced facilitation of muscarinic firing, it would not account for the selective action of VIP on muscarinic transmission or the enhancement of muscarinic ganglionic depolarization. The latter action is more likely to be attributable to an alteration in agonist muscarinic receptor interaction, as has been demonstrated for VIP effects in the salivary gland (*3*), or to a synergistic action on the ionic channels involved in the slow muscarinic depolarization. In sympathetic ganglia muscarinic agonists act on M-channels to decrease membrane conductance to potassium ions and produce depolarization (*19*). VIP elicits a similar decrease in conductance in myenteric ganglion cells (*17*). Thus, an interaction of VIP and muscarinic agonist–induced changes in M-channels could contribute to the observed synergistic effects.

A synergistic interaction between VIP and cholinergic agonists has been noted when monitoring chemical changes in neural and nonneural tissues. For example, the cholinergic agonist carbachol has been reported to enhance VIP-induced increases in cyclic AMP in the cat submandibular gland, VIP-induced secretion of amylase from pancreatic acinar cells, and VIP-induced increases in tyrosine hydroxylase activity in the rat superior cervical ganglion (*5, 20*). These effects of carbachol were blocked by atropine, indicating that they were mediated by muscarinic receptors. Thus, VIP-muscarinic interactions may have an important role at various sites in the autonomic nervous system.

A presynaptic effect of VIP to enhance ACh release has been suggested as another action at cholinergic synapses (*21*). It is unlikely, however, that this effect was involved in the responses in the cat superior cervical ganglion, since VIP did not affect nicotinic transmission and since similar effects of VIP have been noted in ganglia 10 to 14 days after transection of the cervical sympathetic trunk (*22*). Indeed, in these preparations the ganglionic excitatory response of VIP was enhanced and the peptide directly elicited a postganglionic discharge. This was never seen in normal ganglia.

In view of the prominent effect of VIP on sympathetic and parasympathetic ganglia (*4–6*) and the presence of VIP-containing varicosities in ganglia (*7*), there has been interest in the possibility that VIP is a transmitter or neuromodulator at ganglionic synapses. Preganglionic nerve stimulation in the rat superior cervical ganglion increases cyclic AMP (*5*) and tyrosine hydroxylase activity through cholinergic and noncholinergic mechanisms (*23*). VIP duplicates the noncholinergic effects of nerve stimulation and therefore may mediate the response. In addition, VIP could have an indirect effect on ganglionic transmission by influencing muscarinic modulatory mechanisms in ganglia (*4*). It is important to determine whether this interaction between VIP and muscarinic synaptic mechanisms extends to cholinergic synapses at other sites, such as the myenteric plexus and the brain, where VIP-containing pathways are prominent (*24*) and where VIP also has a facilitatory effect on neuronal activity (*25*).

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