respiratory mucosa by asbestos could account for its cocarcinogenic effects in combination with the polycyclic aromatic hydrocarbons in cigarette smoke.

It is unclear how RME prevents hyperplasia and metaplasia, although the retinoid appears to inhibit either cellular division or the synthesis of DNA (or both). In rats, retinoids inhibit the development of squamous lung nodules and carcinomas induced by 3-methylcholanthrene (*5*, *14*) and squamous metaplastic lesions and carcinomas appearing in the urinary bladder after administration of *N*-methyl-*N*-nitrosourea (*3*). These observations and our findings suggest a possible role for retinoids in either the prophylaxis or treatment of respiratory lesions associated with asbestos exposure in man.

B. T. MOSSMAN
J. E. CRAIGHEAD
Department of Pathology, University of Vermont College of Medicine, Burlington 05405
B. V. MACPHERSON
Department of Epidemiology and Environmental Health, University of Vermont College of Medicine

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Retina-Dependent Activation by Apomorphine of Metabolic Activity in the Superficial Layer of the Superior Colliculus

Abstract. *Studies of the effects of the dopamine agonist apomorphine on local cerebral glucose utilization by means of the carbon-14–labeled deoxyglucose method demonstrate a dose-dependent metabolic activation in the superficial layer of the superior colliculus in the rat. Apomorphine stimulated glucose utilization in a number of other cerebral structures, but only the effect in the superficial layer of the superior colliculus depended on an intact retinal input. This effect was present with the animal in the light or in the dark, but was abolished by enucleation, which left the effects in other cerebral structures unimpaired. Activation of the superficial layer of the superior colliculus appears, therefore, to be secondary to an action of apomorphine on dopaminergic systems within the retina.*

The 2-deoxyglucose (2DG) technique for mapping functionally related alterations in glucose utilization in discrete regions of the central nervous system (CNS) is a useful tool for studying the central components of the visual system (*1*). Application of the 2DG technique in primates has provided striking demonstrations of the metabolic organization of the primary visual system (*1*), for example, the ocular dominance and orientation columns described originally on the basis of anatomical and electrophysiological studies by Hubel and Wiesel (*2*). In the rat it has provided evidence of a direct quantitative relationship between the level of sensory input from the retina and the rate of glucose utilization in components of the central visual system (the dorsal lateral geniculate body, the stratum griseum superficiale of the superior colliculus, and the primary visual cortex) (*3*).

The existence of dopaminergic neurons among the amacrine cells of the retina has been demonstrated and characterized by fluorescence histochemistry and morphological techniques (*4*). Although the anatomy (*4*) and pharmacological responsiveness in vitro (*5*) of this system are typical of model dopaminergic systems, the physiological significance of the retinal dopaminergic neurons to the visual process remains obscure. In the course of investigations with the 2DG technique (*6*) on the local metabolic consequences of pharmacological manipulation of cerebral dopaminergic systems, we have obtained results which may provide insight into the role of the retinal dopaminergic system in the processing of visual information.

In the first series of experiments in rats under ambient laboratory lighting conditions (approximately 600 lumen/m^2 at eye level), we examined the alterations of local cerebral glucose utilization associated with apomorphine administration. Apomorphine produced significant dose-dependent alterations in the rate of glucose utilization in a number of regions of the CNS. The rate of local glucose utilization was approximately proportional to the logarithm of the dose of apomorphine in the range of 0.15 to 1.5 mg per kilogram of body weight. Glucose utilization increased in the extrapyramidal system (zona compacta and zona reticulata of the substantia nigra, caudate nucleus, globus pallidus, and subthalamic nucleus) and decreased in the anterior cingulate cortex and the lateral habenular nucleus. Qualitative evidence of stimulation of glucose utilization by apomorphine in structures of the extrapyramidal system has previously been reported by Brown and Wolfson (*7*). In our quantitative studies, however, effects were also observed in central components of the visual system. The administration of apomorphine resulted in marked elevations of metabolic activity within the superior colliculus; no statistically significant effects were observed in other components of the CNS with primary visual functions, that is, the dorsal lateral geniculate body and visual cortex (Table 1).

Table 1. Mean rates (± standard error) of glucose utilization (in micromoles per 100 g per minute) in central components of the intact visual systems of normal animals studied in ambient light. Measurement of glucose utilization was initiated 10 minutes after intravenous administration of apomorphine (1.5 mg/kg).

Structure	Saline (N = 6)	Apomorphine (N = 4)
Visual cortex	92 ± 4	90 ± 2
Dorsal lateral geniculate body	68 ± 3	66 ± 3
Superior colliculus	67 ± 4	96 ± 1*

*Significantly different from saline control groups, t-test for group comparison, $P < .01$.

The rate of local glucose utilization in the primary visual structures is directly related to functional activity within the visual system. Visual stimulation is associated with increased glucose utilization in the visual cortex, superior colliculus, and lateral geniculate body; removal of

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visual input results in reductions in glucose utilization in these structures (*1*, *3*). Therefore, in all subsequent studies, the visual environment of the animals during the experimental period was standardized. The animals were dark-adapted for 150 minutes and then studied in the absence of detectable light (that is, no detectable registration on Kodak Tri-X Ortho film exposed for 12 hours). The administration of apomorphine (1.5 mg per kilogram of body weight, injected intravenously 10 minutes before local cerebral glucose was measured) to animals maintained in the dark resulted in significantly elevated glucose utilization in the superficial and deep layers of the superior colliculus (Table 2 and Fig. 1); the magnitude of the increases was similar to that observed with this dose of apomorphine in rats under ambient fluorescent lighting. Moreover, there were again no significant effects of apomorphine on metabolic activity in the visual cortex or dorsal lateral geniculate body (Table 2). The rates of glucose utilization in each of the primary visual components were bilaterally symmetrical both in saline-treated control animals and in animals that received apomorphine (Table 2).

Table 2. Mean rates of glucose utilization (in micromoles per 100 g per minute) in central components of the visual systems of dark-adapted rats studied in the dark. The animals had been allowed to adapt to darkness for 2½ hours before the experiment. Measurement of glucose utilization was initiated 10 minutes after intravenous administration of apomorphine (1.5 mg/kg).

Structure	Saline (N = 4)			Apomorphine (N = 4)		
	Left	Right	Δ ± S.E.M.	Left	Right	Δ ± S.E.M.
Intact visual system						
Visual cortex	84	85	1 ± 2	72	72	− 1 ± 1
Dorsal lateral geniculate body	67	65	− 3 ± 1	64	64	0 ± 1
Superior colliculus						
Stratum griseum superficiale	67	67	0 ± 1	85*	86*	1 ± 1
Stratum griseum profundum	62	62	− 1 ± 1	89**	91**	2 ± 4
Right eye enucleated						
Visual cortex	62	76	14 ± 3†	58	71	13 ± 2†
Dorsal lateral geniculate body	49	63	13 ± 2†	50	62	11 ± 1†
Superior colliculus						
Stratum griseum superficiale	39	64	24 ± 3††	38	92*	54 ± 7††
Stratum griseum profundum	59	59	0 ± 1	88**	88**	1 ± 1

Comparisons between saline controls and apomorphine treatment, t-test for group comparison: *$P < .05$; **$P < .01$. Comparisons between left and right hemisphere, t-test for paired data: †$P < .05$; ††$P < .01$.

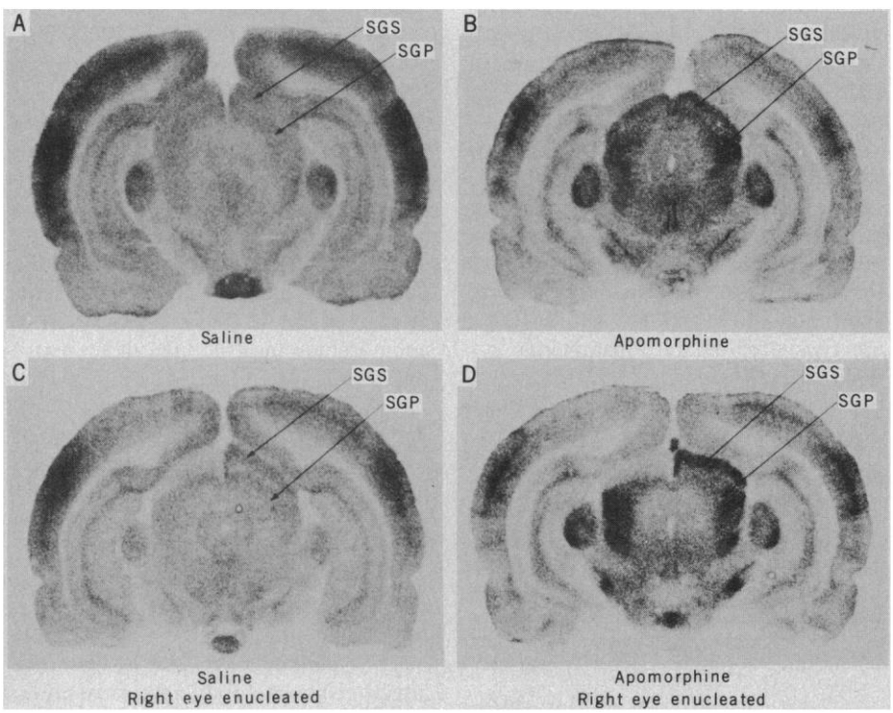

Fig. 1. Representative autoradiographs at the level of superior colliculus in dark-adapted rats studied in the dark. Abbreviations: *SGS*, stratum griseum superficiale; *SGP*, stratum griseum profundum. (A) Saline, intact visual system. (B) Apomorphine (1.5 mg/kg), intact visual system. Note bilaterally increased optical density (that is, elevated glucose utilization) in both superficial and deep laminae of the superior colliculus. (C) Saline, right eye enucleated. Asymmetrical optical density with reduction on contralateral side is apparent within the superficial layer, whereas in the deeper layer optical density remains symmetrical. (D) Apomorphine (1.5 mg/kg), right eye enucleated. Note increased optical density bilaterally in the deeper layer but only in the right or ipsilateral superficial layer of the superior colliculus.

The visual system of the rat is crossed approximately 85 percent at the optic chiasma (*8*). Unilateral blindness thus affords the opportunity to examine in an individual animal the importance of an intact ocular system to the apomorphine-induced increase in glucose utilization in the superior colliculus. In a group of eight rats, the right eye was enucleated under halothane anesthesia, and approximately 4 hours were allowed for recovery from anesthesia before the measurement of local cerebral glucose utilization. Each animal was dark-adapted for 150 minutes before either saline or apomorphine was administered; they were maintained in the dark throughout the remainder of the experiment. Measurement of local cerebral glucose utilization was initiated 10 minutes after the intravenous administration of 1.5 mg of apomorphine per kilogram or an equivalent volume of normal saline.

Unilateral enucleation reduced glucose utilization in all of the contralateral primary visual structures of the control and apomorphine-treated animals, even under the experimental conditions of no detectable light (Table 2). The greatest reductions were observed in the superficial layer of the superior colliculus. Glucose utilization in the deep layer of the superior colliculus was unaltered by unilateral enucleation (Table 2 and Fig. 1). No asymmetry was observed in any region of the CNS other than the primary visual structures. The morphological and functional differences between the superficial and deeper laminae of the superior colliculus have been the subject of detailed investigation for a number of years. It has been generally recognized that the afferent fibers from the retina to the superior colliculus terminate exclusively in the superficial layer, which is also the predominant site of termination of the input from the primary visual cortex. On the other hand, the deeper laminae are the sites of termination of neural systems concerned with the conveyance of nonvisual information from numerous cerebral structures (*9*). Our observations

that glucose utilization in the deeper laminae of the superior colliculus are unaltered by unilateral enucleation (Table 2 and Fig. 1) are consistent with present knowledge of the functional organization of this structure.

The administration of apomorphine to the unilaterally enucleated animals maintained in the dark increased glucose utilization only in the superficial layer of the superior colliculus to which the visual pathway remained intact (Table 2 and Fig. 1). In contrast, apomorphine stimulated glucose utilization equally in the deeper laminae of both superior colliculi, and the response was unaffected by the unilateral enucleation (Table 2 and Fig. 1). Similarly, the alterations in glucose utilization produced in nonvisual structures of the CNS by apomorphine administration were not influenced by the unilateral enucleation.

Although various agents—particularly dopamine, acetylcholine, and γ-aminobutyric acid—have been implicated as possible neurotransmitters in the retina (*10*), the complex synaptic organization of this tissue has impeded the elucidation of the role of each of these agents in the receipt and processing of visual information. The dopamine-containing amacrine cells ramify extensively within the inner plexiform layer and form complex synaptic interconnections with both dopaminergic and nondopaminergic processes (*4*). A dopamine-sensitive adenyl cyclase has been characterized in retinal tissue in vitro (*5*), and the biochemical pharmacological responsiveness of the dopaminergic system in the retina appears to be similar to that of other regions of the CNS (*5*). In contrast, the superficial layer of the superior colliculus has extremely low concentrations of dopamine (*11*), and there is no evidence that it contains dopaminergic receptor systems. Electrophysiological examination of the action of dopamine in the retinal systems has been limited, although it provides some evidence that electrical activity in the retina may be modified by dopamine (*12*). The relation of the retinal dopaminergic system to visual stimuli is not clearly understood, but the rate of synthesis of the amine and its release from the retina are known to depend on experimental lighting conditions (*13*).

We have demonstrated both under ambient laboratory lighting conditions and in the dark that the administration of the putative dopaminergic agonist apomorphine results in increased metabolic activity in the superficial and deep layers of the superior colliculus but not in other primary visual structures in the CNS. Removal of most of the retinal input to one side of the brain by unilateral enucleation abolishes the effect of apomorphine only in the superficial layer of the superior colliculus of the deafferentated side without altering the metabolic effects of apomorphine in the deep layer and elsewhere in the CNS. These results point to the retina as the locus of the action of apomorphine resulting in effects in the superficial layer. They also suggest that the retinal dopaminergic systems function mainly in the retinal pathways to the superior colliculus and not to other primary visual areas.

JAMES MCCULLOCH*
HELEN E. SAVAKI
MAILIS C. MCCULLOCH*
LOUIS SOKOLOFF

Laboratory of Cerebral Metabolism, National Institute of Mental Health, Bethesda, Maryland 20205

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* Present address: University of Glasgow, Glasgow, Scotland G12 8QQ.

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Placental Luteinizing Hormone–Releasing Factor and Its Synthesis

Abstract. *The synthesis of a placental luteinizing hormone-releasing factor (pLRF), which is immunologically, physiochemically, and biologically indistinguishable from synthetic LRF, was demonstrated. The incorporation of ^{3}H-labeled leucine by human placental tissue in vitro into pLRF was determined by purification on carboxymethyl-cellulose and specific immunoprecipitation of the ^{3}H-labeled pLRF. The specific activity of the pLRF released into the medium increased 100-fold from day 1 to day 2 of culture and attained a concentration of 2.84 microcuries per microgram. These data indicate that the pLRF that was released initially was endogenous, whereas that released subsequently reflected synthesis.*

Luteinizing hormone-releasing factor (LRF) is a decapeptide synthesized and stored in the hypothalamus. It acts on the pituitary gland to stimulate the synthesis and release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) (*1*). Recently we found immunoreactive LRF in human placenta by radioimmunoassay and immunofluorescence microscopy (*2*). The immunofluorescence technique revealed that the placental LRF (pLRF) was present in the cytotrophoblast but not the syncytiotrophoblast of the placental villi. The radioimmunoassay indicated that the concentration of pLRF in human placentas varied according to the duration of pregnancy but not the sex of the fetus (*2*). The enormous quantities of pLRF in the placenta led us to suggest that the placenta may be an extrahypothalamic source of this factor during human pregnancy. This hypothesis is supported by a study showing that when placental tissue is cultured in vitro there is a 5- to 40-fold net increase in the concentration of pLRF in the culture medium after 4 days (*3*).

The studies described herein provide direct evidence of the synthesis of pLRF in vitro by the term placenta. Tritiated leucine was incorporated by the human placenta in vitro into a peptide biochemically, immunologically, and biologically identical to LRF.

Human placentas were obtained immediately after normal term deliveries. Placental villi were dissected free of membranes and maternal basal plate.

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