with mitochondria from blight-susceptible corn. Other compounds, such as gramicidin D and decenylsuccinic acid, cause similar volume changes along with an associated reduction in the coupling capacity of the mitochondria (*10*). Unpublished research from this laboratory shows that these are general mitochondrial effects and are not dependent on the mitochondria being from susceptible or resistant corn. It is probable that permeability changes are responsible for, or are correlated with, a reduction of coupling efficiency. The pathotoxin-induced rapid swelling of isolated mitochondria is independent of respiration (Fig. 2). Mitochondria swelled (KCl influx) after addition of pathotoxin under both passive and active conditions. This again corresponds to our previous experience with gramicidin D (*10*), with the exception that when pathotoxin-induced swelling was complete the addition of substrate would not cause a contraction as it did when the swelling was induced by gramicidin D.

Several important conclusions emerge from the data. First, the mitochondria isolated from blight-susceptible corn were adversely affected by pathotoxin from *H. maydis* race T, while no such effects were observed in mitochondria isolated from blight-resistant corn. Since the type of cytoplasm seems to be the determining factor in susceptibility or resistance of corn plants to race T of the southern corn blight fungus, mitochondria, with their inheritance capacity, could be a primary site of pathotoxin effect. The importance of mitochondrial respiration and production of adenosine triphosphate to the functioning of the whole plant is without question. The lack of functional mitochondria would spell quick death to diseased cells. Second, the effects of the pathotoxin on isolated mitochondria are in all instances concerned with membranes. Such a finding leaves the door open to comparable research involved with a myriad of biological reactions associated with the plasmalemma and membranes of other cytoplasmic organelles. In short, the research reported here is merely an introduction to a much more detailed study of the effects of the pathotoxin from *H. maydis* race T on cytoplasmic structure and function.

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Superior Colliculus: Some Receptive Field Properties of Bimodally Responsive Cells

Abstract. *Many cells in the intermediate and deep gray layers of the superior colliculus of the cat respond to both auditory and visual stimuli. These cells have similar receptive fields for both modalities and are directionally selective for both modalities, requiring stimuli moving laterally away from the animal. Perhaps cells that integrate auditory and visual information participate in the control of orienting and following responses to stimuli of both modalities.*

Several anatomical and physiological studies have suggested that the mammalian superior colliculus is primarily involved in the processing of visual information. The superficial gray and optic layers (superficial layers) of the cat superior colliculus receive both crossed and uncrossed projections from the optic nerve and an ipsilateral projection from the visual cortex (*1*). Cells in these layers have well-defined visual receptive fields (*2*).

The colliculus may also be involved in the processing of auditory and somatosensory information. The intermediate and deep gray layers (deeper layers) receive ascending projections from the inferior colliculus, spinal cord, and trigeminal nuclei (*3*). The deeper collicular layers also receive descending input from temporal cortex and postcentral gyrus (*4*). In the intact, unanesthetized cat, auditory and somatosensory stimuli drive a large number of cells in the deeper collicular layers (*5*). The stimuli required to drive these cells have not, however, been studied in detail.

I have found that if a cell responds to both auditory and visual stimuli, several of the receptive field properties are similar for both modalities. In particular, most cells responding to auditory and visual stimuli are directionally selective in response to both stimulus modalities, that is, they respond better to movement of the stimulus in one direction than to movement in the opposite direction. For both modalities, the horizontal component of the preferred direction was toward the periphery of the contralateral field.

An animal was prepared for recording several weeks before the actual experiment. Under Nembutal anesthesia, a well with a screw-on cap was implanted in the skull overlying the superior colliculus. At the same time, four bolts were cemented into the skull anterior to the plug. On the day of the experiment, the animal was anesthetized with halothane and nitrous oxide, intubated, and placed in a Horsely-Clarke stereotaxic apparatus facing a tangent screen. Supports were attached to the bolts, and the eye, ear, and mouth bars were removed. Thus, no pressure points or open wounds were present during recording; anesthesia could be discontinued. The animal was paralyzed with a mixture of gallamine and tubocurarine (*6*) and artificially respired. These experiments required the use of unanesthetized animals because previous experiments have shown that sensory stimuli do not drive cells in the deeper layers of the superior colliculus of anesthetized cats (*7*).

The cap was then removed from the well and a tungsten microelectrode (*8*) was lowered through the well to the superior colliculus. When the electrode isolated a single unit, a variety of visual, auditory, and somatosensory stim-

uli was presented to the animal in attempts to drive the unit.

Visual stimuli consisted of a variety of light and dark shapes projected onto the screen. Background illumination for light stimuli was 0.0 to 0.5 log cd/m^2, and the stimuli were about 0.5 to 1.5 log units brighter. For dark stimuli the background was 0.5 to 1.5 log cd/m^2, and the stimuli were 0.5 to 1.5 log units dimmer.

Auditory stimuli were pure tones, tone sweeps, and a variety of complex noises. Auditory stimuli were moved by hand, and the eyes were occluded during their presentation. Ambient sound level in the laboratory (measured at the position of the cat's ears) was about 68 db. Tones between 300 hz and 8 khz had a maximum intensity of about 86 db. The maximum intensity of the complex sounds varied between 70 and 88 db. Other details of the techniques of stimulating and recording have been described elsewhere (*7*).

Most electrode tracks were marked by one or more electrolytic lesions. The brain was perfused with 10 percent formalin, embedded in celloidin, sectioned serially, and stained with cresyl violet. The small electrolytic lesions were used to reconstruct the electrode tracks and the positions of the units within the laminae.

Two hundred and six cells were studied in these experiments. One hundred and eight were in the superficial layers and 98 in the deeper layers. Most visually driven cells in all layers had receptive fields in the contralateral visual field. They responded well to moving line stimuli (slits, bars, edges, and tongues), were binocularly driven, and were directionally selective. Directionally selective visual responses never showed a reversal of preferred direction when the leading edge of the stimulus was changed from black to white. For most cells, however, the directional selectivity was not very precise. Cells frequently responded well over a wide range of directions and failed to respond only if the horizontal component of the movement was toward the vertical midline of the visual field. Most commonly, the best response was obtained to horizontal movement away from the vertical midline.

The deeper layer cells had much larger receptive fields than did more superficial cells. The smallest receptive field of a cell localized in the intermediate or deep gray was 7° wide and 5° high (35 square degrees). Forty out

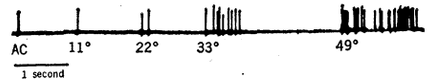

Fig. 1. Responses of a unit in the intermediate gray layer of the superior colliculus of the cat that responded to stationary auditory stimuli. The tangent screen was tapped with a wooden stick at several positions along the horizontal meridian of the visual field. The response increased as the stimulus moved away from the area centralis (*AC*) into the contralateral field. Stimuli in the ipsilateral field evoked no responses. (Traces retouched from storage oscilloscope.)

of 84 cells localized in the superficial layers had receptive fields smaller than 35 square degrees. Thirty out of 72 deeper layer cells, whose visual receptive fields were mapped in detail, responded to the entire tangent screen area contralateral to the medial receptive field border. In all experiments, the animal was placed so that the medial receptive field border was at least 20° from the peripheral edge of the

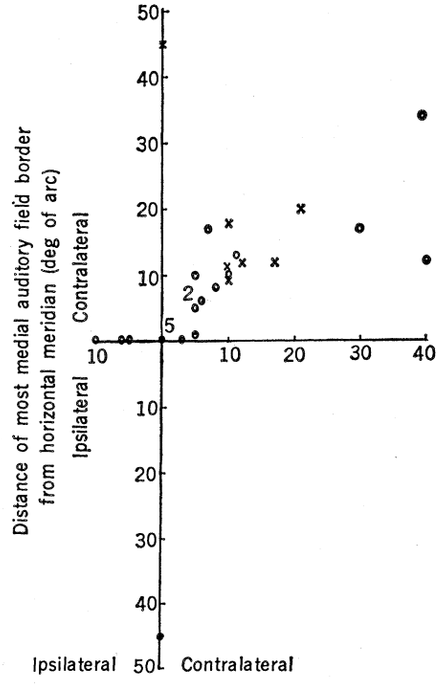

Fig. 2. Relation between visual and auditory receptive field positions of deeper layer collicular units. The circles represent bimodal units. The point at the origin represents five units. The point at (6,6) represents two units. All other points represent one unit each. The crosses represent units responding only to auditory stimuli. The position of the visual receptive field was taken to be that of the nearest unit responding to visual stimuli.

screen. These large receptive fields did not have sharp borders; the response of the cell decreased gradually as the stimulus moved away from the most sensitive portion of the field.

Deeper layer cells also responded to a wider variety of stimulus shapes and sizes than did superficial cells. Many deep layer cells responded equally well to stimuli 2° high and to stimuli 20° or 30° high. Deeper layer cells were also frequently difficult to drive consistently, that is, their excitability varied from moment to moment.

The most striking change encountered as the electrode entered the intermediate gray was the presence of units responding to auditory and, less frequently, to somatosensory stimuli. Eighty of the 98 deeper layer units responded to visual or auditory stimuli but not to somatic stimuli. Seventeen of these 80 units responded only to visual stimuli, 6 responded only to auditory stimuli, and 57 responded to both auditory and visual stimuli.

Most of the units responding to auditory stimulation responded well to complex sounds. The hiss made by air moving through a partially constricted hose was particularly effective. The pure tones and tone sweeps were usually ineffective.

A cell responded to an auditory stimulus only if that stimulus was moved through certain portions of the auditory field (Fig. 1). For convenience, the angular position of the auditory receptive fields is described with the area centralis of the contralateral eye as a reference point. If a cell responded to both auditory and visual stimuli, the positions of the auditory and visual receptive fields were highly correlated. Because the responses were quite variable, and because neither the visual nor auditory fields had sharp borders, it was rarely possible to determine whether or not all the borders of the visual and auditory fields corresponded. For 22 cells, however, the positions of the medial borders of both the auditory and visual fields could be mapped quite precisely (to within about 3°). For these bimodally responsive cells, the correlation between the position of the medial border of the visual receptive field and the position of the medial border of the auditory receptive field was .68 ($P < .001$, two-tailed). The position of the medial receptive field border of a cell responding only to auditory stimuli was highly correlated with the medial receptive field bor-

der of the nearest visually responsive cell (Fig. 2). The existence of occasional cells with receptive fields in the ipsilateral field provides additional evidence for the correspondence of auditory and visual receptive fields. I recorded from four bimodally responsive cells that had visual receptive fields extending more than 10° into the ipsilateral field and less than 3° into the contralateral field. For each of these cells the auditory receptive field was primarily within the ipsilateral field.

For some cells, however, the medial borders of the auditory and visual fields clearly did not coincide (Fig. 2). A few cells responded to the entire contralateral auditory field, including areas lateral and posterior to the visual fields.

Most cells responded only to moving visual and auditory stimuli and were directionally selective in response to both modalities. For 39 cells I was able to determine the directional selectivity for each modality. Twenty-six were directionally selective for both modalities; six were directionally selective only for visual stimuli; seven were not directionally selective for either modality. For both modalities, the horizontal component of the preferred direction was always toward the periphery of the contralateral field (Fig. 3). Although the optimum direction of movement was the same for both modalities, the precise range of directions over which the cell responded was not always identical for both. For example, the cell whose responses are illustrated in Fig. 3 was more responsive to auditory than to visual stimuli and also responded to auditory stimuli over a wider range of directions of movement.

The anatomical inputs responsible for the directional selectivity of the auditory responses are not known. These responses might, like the directionally selective visual responses (*9*), be elaborated from the responses of cortical cells. Alternatively, the occasional directionally selective cells in the inferior colliculus (*10*) might provide cells in the superior colliculus with directionally selective input.

The existence of cells with directionally selective responses to two modalities supports prevalent notions regarding collicular function. The effects of collicular lesions have suggested that the colliculus is involved in following and orienting responses to visual, auditory, and tactile stimuli (*11*). The cells described here can integrate information from more than one sensory modality; they are driven by both visual and auditory stimuli that are moving laterally away from the animal. Perhaps they provide information that will enable an animal to visually track a stimulus regardless of the modality with which that stimulus first impinges upon the animal. Such cells might, therefore, control head, eye, or body movements. Alternatively, these cells may not direct movements. They may merely receive the information that the paralyzed animal has attempted to follow a moving stimulus and has failed to do so. These possibilities can be distinguished only by studying cells of this type in unparalyzed animals trained to follow moving visual and auditory stimuli.

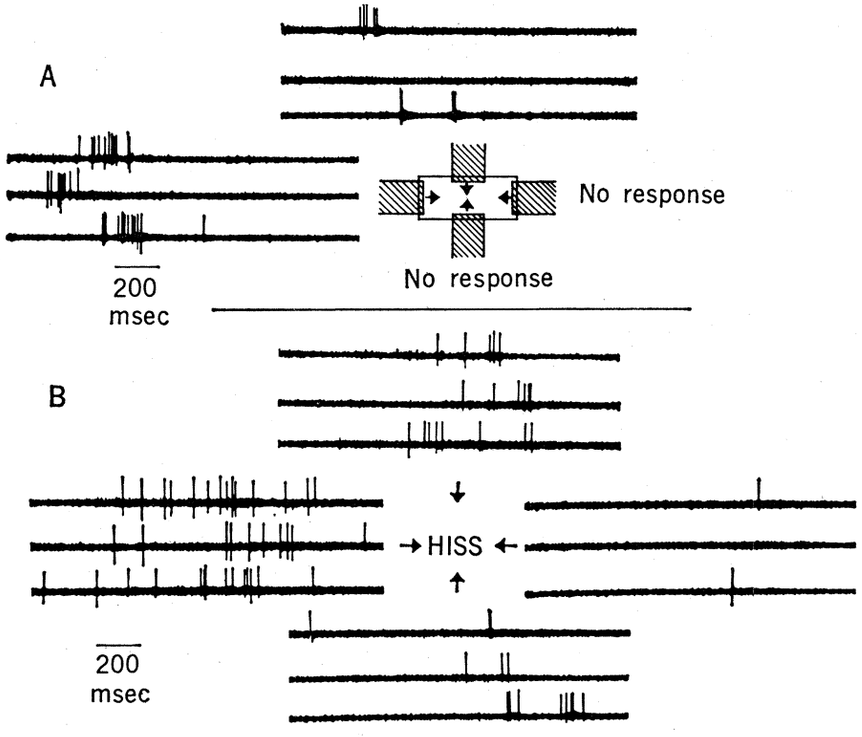

Fig. 3. Responses of a unit in the intermediate gray layer of the superior colliculus to visual (A) and to auditory (B) stimuli. The visual receptive field was 10° wide and 4° high. The visual stimulus was a 3° dark tongue moved through the receptive field in the direction indicated by the arrow. The auditory stimulus was the hiss of a partially constricted air hose moving across the area of the visual receptive field in the direction indicated by the arrow. (Traces retouched from storage oscilloscope.)

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Delta-9-Tetrahydrocannabinol: Metabolism and Disposition in Long-Term Marihuana Smokers

Abstract. *Radioactively labeled delta-9-tetrahydrocannabinol (Δ^9THC) administered intravenously to chronic marihuana smokers disappeared from the blood plasma with a half-life of 28 hours as compared to 57 hours for nonusers of marihuana. Apparent volumes of distribution did not significantly differ between the two groups. Within 10 minutes after administration of Δ^9THC, 11-hydroxy-Δ^9THC is present in the plasma of nonusers and chronic users. This metabolite was also present in urine and feces of nonusers and long-term marihuana smokers. In addition, polar metabolites were excreted in urine and feces of both groups for more than 1 week.*

Previous studies (*1*) have shown that ^{14}C-labeled Δ^9-tetrahydrocannabinol (Δ^9THC) persists in the plasma of human subjects for several days and is excreted in urine and feces for more than 8 days. The subjects in those experiments were normal volunteers who had no previous exposure to *Cannabis* preparations. We now report the effects of long-term marihuana smoking on the disposition and metabolism of [^{14}C]Δ^9THC.

Five male subjects (*2*), ranging in age from 21 to 27 years old, who professed smoking marihuana daily for a minimum of 1 year immediately before this investigation were used. The subjects appeared to be reliable and conscientious. Three were upper-level college students, and the other two were college graduates who were gainfully employed. None of the subjects used any other drugs or medications. The subjects were evaluated medically and psychiatrically before being considered for this study. They smoked marihuana as usual the evening before the study but did not during the study. On the morning of admission, 0.5 mg of [^{14}C]Δ^9THC was administered intravenously (*3*) and blood samples were drawn at intervals thereafter. Urine and feces were collected for 7 days after injection of the radioactive compound.

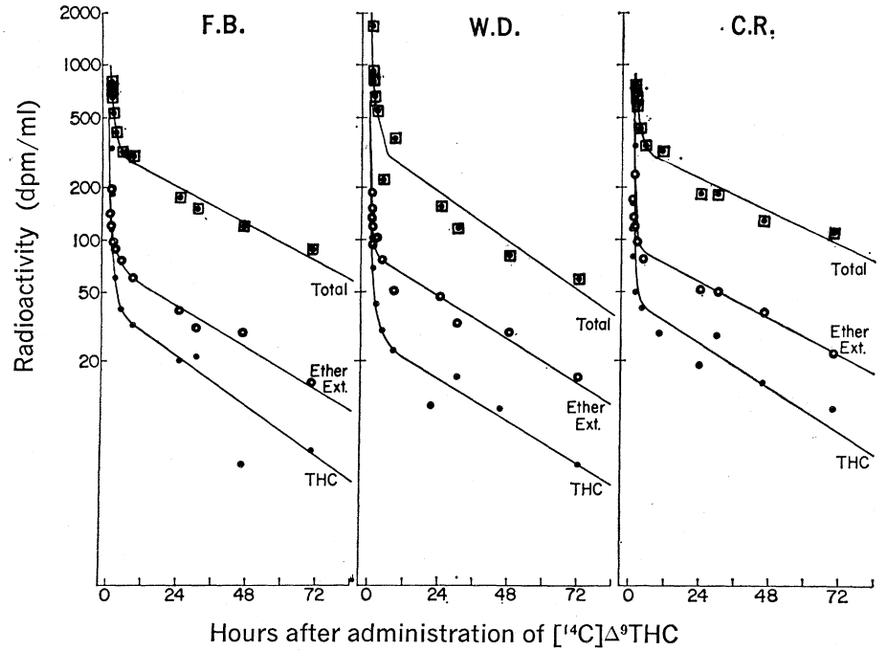

Fig. 1. Plasma levels of Δ^9THC, total radioactivity, and ether-extractable radioactivity after the intravenous injection of [^{14}C]Δ^9THC. Three long-term *Cannabis* users received 0.5 mg of Δ^9THC in 1 ml of ethanol. The radioactive solution was injected during an interval of 1 minute into the tubing of a rapidly flowing intravenous infusion of 5 percent dextrose in water. At intervals, blood samples were drawn from the opposite arm into syringes containing heparin. Plasma was assayed for Δ^9THC, total radioactivity, and ether-extractable radioactivity by liquid-scintillation spectrometry.

Intravenous administration of Δ^9THC (0.5 mg) to nonsmokers was devoid of any pharmacological effect. In contrast and admittedly not under well-controlled experimental conditions (since no placebos were administered) all of the long-term marihuana smokers (although told that a nonpharmacological dose of THC was to be given) reported effects that lasted for as long as 90 minutes. One subject stated that he "felt a familiar feeling" reminiscent of the effects of marihuana. The dose of Δ^9THC given to these subjects was in the range of 5 to 7 μg/kg. Kiplinger *et al.* (*4*) have shown that long-term marihuana smokers are able to obtain pharmacologic effects from smoking a marihuana cigarette which delivers a dose of Δ^9THC in the order of 6.25 μg/kg.

Unchanged Δ^9THC was determined in blood plasma by extraction at *p*H 7.4 with four volumes of heptane containing 1.5 percent isoamyl alcohol (*1*). The residual plasma was then extracted with ether to assay less polar metabolites. The more polar metabolites remained in the aqueous phase. The radioactivity was determined by liquid scintillation spectrometry and corrected for quenching by use of internal standards. The recovery of Δ^9THC added directly to plasma or urine was 95 ± 5 percent.

As in the previous study (*1*), the disappearance of Δ^9THC from plasma appeared to occur in at least two phases (Fig. 1). The initial phase was rapid and was followed by a slower phase, which had a half-life ($t_{1/2}$) of 28 hours (Fig. 1 and Table 1). This second phase was considerably more rapid than that found in nonsmokers ($t_{1/2}$ = 57 hours). Chromatography of the apparent Δ^9THC in the heptane extract of plasma obtained from chronic users had the same R_F as authentic Δ^9THC (*5*). In addition, small amounts of 11-OH-tetrahydrocannabinol were present