short latencies of the CW + ECS + PFS group are consistent with the previously reported ECS-induced amnesia for this task (*8*). The potential of noncontingent FS to induce recovery of memory of ice water is demonstrated by the CW + ECS + FS group. The long latencies evident in this group suggest that amnesia was largely, if not totally, reversed. Such data support the hypothesis that ECS hampers retrieval but does not destroy the memory of recently learned information. Furthermore, the return of memory was specific to the training situation and not merely a change in activity level. Lack of avoidance in the NCW + ECS + FS group demonstrates that the long latencies of the CW + ECS + FS group were not a function of a reduction in mobility level due to the interaction of ice water, ECS, and FS.

Inhibition of the step-through response by the CW + ECS + FS group indicates that noncontingent FS has reactivated a retrieval mechanism for memory of training with ice water. This study, as well as others which have reversed the amnestic effects of ECS or cycloheximide, indicate that at least these two amnestic agents interfere with retrieval mechanisms rather than, or in addition to, disrupting storage processes. Alternative interpretations of experimental amnesia produced by ECS ordinarily invoke a consolidation (storage) impairment model in which information is either prevented from entering long-term storage or is stored in a degraded form. However, such a model cannot explain reversal of amnesia induced by a noncontingent recovery agent which was quite dissimilar from any stimulus present during the training trial. As relevant information was not available during the recovery event, any memory present at the time of testing must have been previously present but unavailable. Regardless of the quality of the memory that is stored following ECS, it is nevertheless apparent that ECS disrupts retrieval of such memories rather than completely blocking their storage. Moreover, it is difficult to support the assumption that ECS ever prevents or distorts the storage of recently acquired information on the basis of present data. Recovery from experimental amnesia is clear evidence for retrieval failure, whereas a failure to reverse amnesia is not unambiguous proof of a consolidation impairment. Inability to produce recovery of memory following ECS is always potentially a function of using inappropriate recovery agent parameters. Conclusive evidence of a consolidation failure requires that the specific structural form of a memory be identified in trained animals as well as being found absent in amnestic animals.

The reversal of amnesia produced in the present experiment using different training and recovery stimuli parallels the reversal of cycloheximide-induced amnesia (*5*). Previous reports of recovery from ECS-induced amnesia has tended to refer to the recovery agent as a "reminder" (*4*). A cognitively oriented model underlying the term "reminder" assumes that specific features of the recovery agent reactivate memories of prior events similar to the recovery event, explicitly, those of training. Consequently, noncontingent FS was previously used to remind amnestic animals of prior training with FS (*3, 4*). The present data require a revision in the concept of "reminder," since noncontingent FS assumedly possesses few physical properties in common with ice water and is yet able to restore memory of prior training with ice water. These data should not be misconstrued as suggesting that the recovery agent can be totally dissimilar from the training event and yet be able to induce recovery of memory. Instead, FS may effectively restore memory of training with ice water because these two agents have similar arousal properties. This explanation is in effect a generalization of the "reminder" position, and is consistent with the recovery of FS memories from cycloheximide-induced amnesia achieved with amphetamine and corticosteroids (*5*).

Because of the gross neural discharges triggered by ECS, it is most improbable that any information uniquely encoded in the format of electrochemical transmission survives the neural seizure. Therefore, information retained after ECS must necessarily be at least partially encoded in a less vulnerable form than neural transmission. In the present experiment ECS onset followed initial contact with ice water by 10 seconds. Since memory of training proved recoverable, this interval defines a maximal consolidation time necessary for one-trial passive avoidance of ice water immersion. Moreover, this brief interval is consistent with the less than 500 msec consolidation interval previously reported in a study using a familiarization paradigm (*9*).

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7 April 1972; revised 1 June 1972

Axonal Transport of Gangliosides in the Goldfish Optic Nerve

Abstract. *Radioactive glucosamine and* N-*acetylmannosamine injected into the goldfish eye are incorporated into gangliosides that undergo rapid axonal transport to the optic nerve terminals. All ganglioside fractions are labeled. These data provide the first evidence that axonal transport has a role in neuronal ganglioside function and metabolism.*

The brain contains a high concentration of ganglioside compared to other tissues (*1*) and appears to be the only organ with more of its sialic acid in lipid-bound form (that is, in ganglioside) than in glycoprotein (*2*). Gangliosides occur at low concentrations in isolated astrocytes (*3*), oligodendroglia (*4*), neuronal perikarya (*3*), and myelin (*5*), while in contrast they show considerable enrichment in the synaptosomal and microsomal fractions (*6*). The source of nerve-ending ganglioside poses an intriguing and still unsolved problem. Local synthesis is one possibility in view of evidence for the presence of glycosyltransferase enzymes in synaptosomal fractions (*7*). However, cell-body syn-

thesis followed by axonal transport also requires consideration. Forman *et al.* (*8*) have shown that glycoproteins assembled in neuronal perikarya are conveyed to the nerve endings by rapid axonal transport. In that study amino sugar precursors were also incorporated into transported materials that were soluble in chloroform : methanol. In this report we identify the constituents extracted in this solvent system as gangliosides and establish their rapid axonal transport to nerve terminals.

The goldfish optic system was employed as described (*9, 10*). Radioactive precursors injected into the eye are incorporated into molecules in the retinal ganglion cells, and those which undergo axonal transport are detected in the contralateral optic tectum where the axons terminate. This tectum may also contain labeling due to local incorporation of precursor that has leaked from the eye and reached the brain through the bloodstream. Such background labeling is measured in the ipsilateral tectum (which receives no fibers from the injected eye) and must be subtracted to calculate the amount of transported radioactivity.

Labeled amino sugars were injected in 5 μl of physiological saline into the eyes of goldfish (*Carassius auratus*) with a Hamilton microliter syringe. In the first experiment each of 43 fish was injected in the right eye with 12.3 μc of D-*N*-[^{3}H]acetylmannosamine (1020 mc/mmole), and in the second each of 49 fish received 5.2 μc of D-[6-^{3}H]glucosamine (3600 mc/mmole) in the right eye and 1.2 μc of D-[1-^{14}C]glucosamine (59 mc/mmole) in the left eye (*11*). Twenty-four hours after injection the fish were decapitated and the tecta were removed by dissection. Pooled left and right tecta were extracted separately with approximately 30 volumes of chloroform : methanol (1 : 1) followed by an equal volume of these solvents (1 : 2). The extracts were filtered through sintered glass funnels of medium porosity and the combined filtrates evaporated to dryness with a nitrogen stream in 10-ml centrifuge tubes.

Gangliosides were isolated and purified by the following procedure, specific activity being determined at the four stages indicated (Table 1). (i) The crude lipid was dissolved in 8 ml of chloroform : methanol (2 : 1) and partitioned twice with aqueous 0.12*M* NaCl by the method of Folch *et al.* (*12*). The combined upper phases contained more than 90 percent of total extracted ganglioside. (ii) The material in the upper phase was incubated with a mixture of phosphodiesterase and alkaline phosphatase (*11*) at specified conditions (*13*) to degrade sugar nucleotides and permit their removal by dialysis. Following incubation, the bulk of protein and salt was precipitated by addition of ten volumes of chloroform : methanol (1 : 1). The filtrate was evaporated and the residue was dissolved in dilute ethylenediaminetetraacetic acid (sodium salt) and dialyzed. (iii) A 1-g column of DEAE Sephadex (A-25) (*11*) was converted to acetate form and used as described (*14*). The above-mentioned sample was applied in chloroform : methanol : water (30 : 60 : 8), and after lipid impurities were eluted with more of the same solvent gangliosides were eluted as a group with chloroform : methanol : 0.8*M* sodium acetate (30 : 60 : 8). The residue from evaporation of the latter fraction was treated for 2 hours with a few milliliters of 0.1*M* NaOH in methanol at 30°C, then diluted with water and dialyzed. (iv) The solid remaining after evaporation of the bag contents was chromatographed on a 1-g column of Unisil (*11*). Impurities were removed with 150 ml of chloroform : methanol (85 : 15), and gangliosides were then eluted with 150 ml of redistilled solvent (2 : 3). Radioactivity was measured by drying portions on filter paper and combusting the latter in a Packard model 305 sample oxidizer for liquid scintillation counting. Sialic acid was quantified by a gas-liquid chromatography method (*15*); since the base treatment removed *O*-acetyl groups attached to sialic acid (*16*), the latter was all in the form of *N*-acetylneuraminic acid.

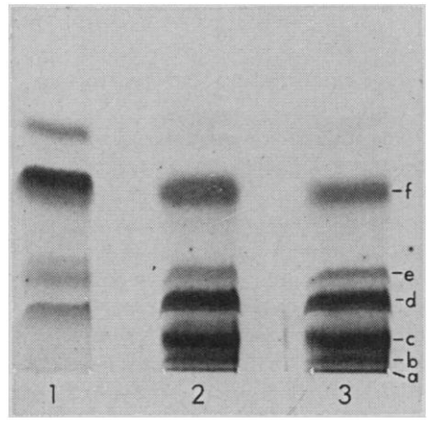

Fig. 1. Thin-layer chromatographic separation of goldfish tectal gangliosides labeled with D-[6-^{3}H]glucosamine. Samples were applied to plates coated with 250 μm of silica gel G (Analtech, Newark, Delaware), and the plate was developed twice with chloroform : methanol : 2.5*N* NH_4OH (60 : 40 : 9) and sprayed with resorcinol. Columns are 1, beef brain gangliosides (standard); 2, right tecta (ipsilateral); and 3, left tecta (contralateral). The individual bands were scraped from the plate and combusted for counting (without prior elution), and the left-right difference was computed. The distribution of transported counts (in percentages) was a, 1; b, 5; c, 53; d, 32; e, 4; and f, 4. All bands were purple except f, which was yellow-brown with a purple tinge. The latter contained a ganglioside and an additional constituent. In propanol : water (70 : 25) the yellow band migrated ahead of all gangliosides and contained no counts.

Table 1. Specific activity of tectal gangliosides at successive stages of purification, following injection of indicated precursor. D-[1-^{14}C]-Glucosamine was injected into the left eyes and the other two precursors into the right eyes. Values are expressed as disintegrations per minute per microgram of *N*-acetylneuraminic acid; U.P., upper phase.

Purification stage	Left (L)	Right (R)	Transported
D-N-[^{3}H]Acetylmannosamine			(L-R)
i. Folch U.P.	453	203	250
ii. Dialyzed U.P.	276	2	274
iii. DEAE Sephadex	266	3	263
iv. Unisil	277	3	274
D-[6-^{3}H]Glucosamine			(L-R)
i. Folch U.P.	2066	795	1271
ii. Dialyzed U.P.	1410	291	1119
iii. DEAE Sephadex	1611	304	1307
iv. Unisil	1575	302	1274
D[1-^{14}C]Glucosamine			(R-L)
i. Folch U.P.	313	575	262
ii. Dialyzed U.P.	92	275	183
iii. DEAE Sephadex	113	300	187
iv. Unisil	104	289	185

The contralateral-ipsilateral difference of the purified fractions, representing specific activity of transported gangliosides, was significantly higher than background incorporation in all three experiments (Table 1). This difference did not change appreciably throughout the course of purification although absolute amounts of radioactivity and sialic acid did decrease; the greatest reduction of radioactivity occurred between stages (i) and (ii) and indicated loss of small molecules. Approximately 75 percent of the sialic acid measured in the crude upper phase was recovered in purified ganglioside. With the purification procedure we were able to eliminate small quantities of sialoglycoprotein which were initially solubilized by extraction with chloroform : methanol. Glucosamine was incorporated

somewhat more efficiently than *N*-acetylmannosamine, but the latter had the advantage of producing much lower background labeling (*17*).

The average yield of purified tectal ganglioside was approximately 0.70 μmole of sialic acid per gram of fresh tissue, which is slightly below the value previously reported for gangliosides of whole goldfish brain (*15*); the material in the earlier study was not extensively purified. Our value is somewhat lower than those reported for other types of fish (*16, 18*). After thin-layer chromatography, the pattern of tectal gangliosides (Fig. 1) was similar to that reported for gangliosides of whole fish brain (*16, 18*). This differs from the typical mammalian pattern in the predominance of slow-migrating bands, which were identified as tri-, tetra- and pentasialo species (*16, 18*). Individual bands that we obtained from both groups of tecta were scraped from chromatography plates and counted after combustion. Bands c and d (Fig. 1) contained 53 and 32 percent, respectively, of total transported counts. With all three precursors the bands were labeled in approximate proportion to resorcinol-staining intensity (band f is discussed in legend to Fig. 1). This proportionality was confirmed by autoradiography of samples labeled with D-[1-^{14}C]glucosamine. Virtually no radioactivity was found outside the ganglioside bands, and the origin had only 1 percent of transported counts. In each experiment the gangliosides from control tecta showed almost the same percentage of distribution of radioactivity as did those from contralateral tecta, although the absolute amounts were significantly less. Thin-layer chromatography plates developed with propanol : water (70 : 25) gave a somewhat different pattern of ganglioside bands, and all fractions migrated farther from the origin; however, counts appeared proportional to resorcinol color. We conclude from these experiments that rapid axonal transport is characteristic of all ganglioside types in the goldfish retinotectal system and not of selective fractions.

In order to compare the quantities of *N*-acetylmannosamine incorporated into transported glycoprotein and ganglioside, the residues after lipid removal from pooled left and right tecta were each washed twice with a cold solution of 10 percent trichloroacetic acid (TCA) and 0.5 percent phosphotungstic acid and counted after combustion. The left-right difference for protein was 329 disintegrations per minute (dpm) per tectum compared to 504 dpm for ganglioside.

The transported gangliosides found in the tecta 1 day after injection must move in the rapid component of axonal transport, because slowly transported materials would not appear in the goldfish tectum until 2 to 3 weeks later (*8, 9*). This conclusion is supported by the finding of Forman *et al.* (*8*) that glycoprotein and lipid—substances labeled with glucosamine—move only at the rapid rate. This rate was estimated at 70 to 100 mm/day for the optic nerve of the goldfish at 23°C (*10*). An alternative explanation of our results—that is, rapid transport of precursor followed by local synthesis in the nerve endings—seems very unlikely in view of the observations of Forman *et al.* (*8*). They found a small amount of transported TCA-soluble radioactivity that appeared with the fast component, but this material arrived somewhat later than the transported glycoprotein and glycolipid and was at all times too small in quantity to account for labeled material by means of local synthesis. Additional support came from the observed effects of acetoxycycloheximide.

While this study demonstrates axonal transport of gangliosides it provides no indication whether local synthesis also occurs in the nerve ending as a concurrent mechanism. In addition to nerve endings, the goldfish tectum contains cell bodies which could account for the background incorporation observed. Isolated synaptosomes from mammalian brain have been reported to incorporate monosaccharides into gangliosides (*19*), although the possibility of contaminating structures usually requires cautious evaluation of such results. Additional studies (*20*) suggested local modification of the carbohydrate residues of glycoprotein acceptors brought to the nerve ending by axonal transport, and a similar mechanism is conceivable for gangliosides. Further studies are needed to assess the relative importance of local synthesis as compared with the transport mechanism in brain ganglioside metabolism.

Note added in proof: After this report was submitted for publication, a paper appeared on gangliosides of the rabbit optic system which claimed no transport of these substances (*21*). Although variation between species is always a possibility in such phenomena, we believe the results of the rabbit study are consistent with our own data for the goldfish; the appearance of labeled ganglioside in the rabbit optic nerve 1 day after intraocular injection of precursor can be interpreted as evidence for rapid axonal transport.

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barrier and cell permeability are more likely to be contributing factors. The difference in background labeling for the two types of glucosamine was probably due to the fact that a greater amount of D-[1-^{14}C]glucosamine was injected and this resulted in proportionately greater leakage into the circulation.

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20 March 1972

Intravenous Injection in Man of Δ^9-Tetrahydrocannabinol and 11-OH-Δ^9-Tetrahydrocannabinol

Abstract. *A microsuspension of Δ^9-tetrahydrocannabinol and of its metabolic derivative 11-OH-Δ^9-tetrahydrocannabinol has been prepared with 25 percent human serum albumin as the vehicle. Intravenous infusion of this preparation to humans indicates that both tetrahydrocannabinols are equally potent in producing the typical marihuana-like pschological and physiological effects.*

There is controversy as to whether the active principle of marihuana is Δ^9-tetrahydrocannabinol (Δ^9THC) or its 11-hydroxylated metabolite (11-OH-Δ^9THC). Christensen *et al.* (*1*) found that 11-OH-Δ^9THC was twice as potent in producing specific neurologic and behavioral responses when injected intravenously to mice than its parent compound. Based on this finding, they suggested that the 11-OH-Δ^9-THC might be the active form of the compound. The scarcity of 11-OH-Δ^9-THC has prevented the study of its pharmacological activity in man. Having available only very small quantities of material (*2*), the intravenous route is mandatory because the oral administration of the drug would require larger amounts to produce significant effects. To our knowledge, the intravenous administration of Δ^9THC or any one of its metabolic derivatives in doses capable of producing physiological and psychological effects in humans has not been performed because of the lack of a suitable intravenous preparation. Thus, although Lemberger *et al.* (*3*) have injected ^{14}C-labeled Δ^9THC intravenously dissolved in absolute ethanol, they only used tracer doses (0.5 mg). Larger doses of the drug requiring larger volumes of absolute ethanol cannot safely be injected into man because they can cause vein irritation, hemolysis, and precipitation of the plasma proteins.

We hypothesized that, if tetrahydrocannabinols could be suspended in human serum albumin and if the particle size of such a suspension were to be smaller than 0.22 μm (the pore size of filters used to sterilize solutions), a safe and easy method for intravenous administration would be available. After experimentation with different proportions of the tetrahydrocannabinols and the human serum albumin, we found the following preparation satisfactory.

Ten milligrams of either Δ^9THC or 11-OH-Δ^9THC dissolved in 0.5 ml of absolute ethanol were pipetted into a beaker containing 50 ml of 25 percent human serum albumin being vigorously stirred magnetically. Since stirring produced considerable foaming of the serum albumin, the suspension was transferred to tubes and centrifuged for 30 minutes. The preparation was then placed in a 50-ml syringe and filtered through a 0.22-μm Millipore filter into a vial and stored until used. All of the glassware utilized was sterile. Empirically, we found that filtration at a rate of 0.92 ml/min with a Harvard constant infusion pump as a source of pressure was satisfactory.

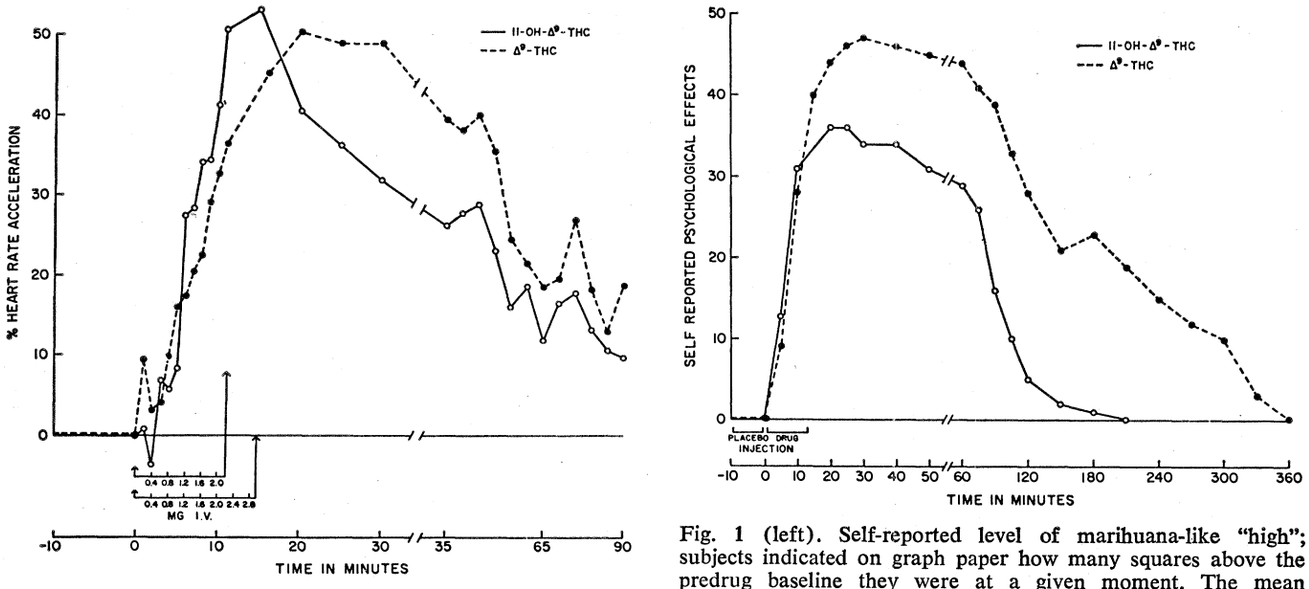

Fig. 1 (left). Self-reported level of marihuana-like "high"; subjects indicated on graph paper how many squares above the predrug baseline they were at a given moment. The mean values of the two groups are illustrated and indicate that the intravenous administration of Δ^9THC produced a more intense and long-lasting psychological experience ($P > .05$) than that produced by its 11-hydroxylated metabolite; *I.V.*, intravenous. Fig. 2 (right). Both Δ^9THC and 11-OH-Δ^9THC produced a significant increase in heart rate. The magnitude of the percentage of heart rate acceleration produced by either one of the compounds is statistically undistinguishable.