response to reserpine, and compared the time course of adaptations in both ChU and ChA.

Male Wistar rats (150–200 g) were injected with reserpine (7.5 mg/kg i.p.). The dose was repeated after 12 h and the rats were killed 14 to 24 h after the first injection. ChA in brain homogenates (10% w/v, 50 mM-sodium phosphate, pH 7.0, 0°C) was assayed radiometrically (Fonnum, 1975). The uptake of [^{3}H]-choline into prism shaped ($0.1 \times 0.1 \times$ approximately 0.5 mm) tissue slices, incubated in Krebs medium (5 min, 37°C) was measured.

Homogenates of corpus striatum from animals treated with reserpine for 20 h showed statistically significant increases in ChA compared with controls (10.1 ± 0.48 to 12.8 ± 0.86 nmol/min, 10 mg protein, $P < 0.01$, $n = 12$). Activities in the cortex, midbrain, hypothalamus, cerebellum, and pons-medulla, however, did not show significant changes ($P > 0.05$). Striatal ChU was increased after 14 h and ChA after 18 h treatment. Increased values were found after 20 h and control values were re-established after 24 h treatment (Table 1).

Thus, the initial adaptation of striatal cholinergic neurones to reserpine involves an increase in ChU. There is a second phase, however, in which the increase in ChU is paralleled by an increase in ChA. This is consistent with the hypothesis that high affinity uptake and subsequent acetylation of choline are coupled in the rat (Barker & Mittag, 1975).

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The effects of chloroquine and other retinotoxic drugs on axonal transport of proteins in rabbit vagus nerve

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Human and animal studies have demonstrated ocular damage as a result of administration of chloroquine and hydroxychloroquine (Nylander, 1967; Shearer & Dubois, 1967), thioridazine (Zinn, 1975), ethambutol (Roberts, 1974) and clioquinol (see Meade, 1975). A number of these drugs, notably thioridazine bear a chemical similarity to chlorpromazine. Since chlorpromazine inhibits the axonal transport of proteins in peripheral nerves through an action on microtubules (Edström, Hansson & Norström, 1973; Cann & Hinman, 1974) we have examined the ability of the above retinotoxic drugs to inhibit the axonal transport of labelled proteins in rabbit vagus nerves *in vitro*.

Vagus nerves with nodose ganglia attached were incubated in medium 199 for 24 h at 38.5°C in a series of two-compartment chambers (McLean, Frizell & Sjöstrand, 1975). Fifteen μCi of tritium-labelled leucine (L-(4,5-3H) leucine, 58 Ci/mmol) were added to the compartments containing the nodose ganglia and a ligature tied on the nerves 6 cm from the ganglia at the start of the experiment. Drugs are dissolved in medium 199 and added to either nerve or ganglion compartment. Tritium-labelled proteins, transported from the nerve cell bodies in the ganglia accumulated in the axons proximal to the ligature. The amount of TCA-insoluble radioactivity in 5 mm segments of each nerve was measured by liquid scintillation counting and expressed as a fraction of the TCA-insoluble radioactivity in the rest of the nerve. Ganglia were homogenized and the TCA-insoluble radioactivity expressed in relation to protein content.

A significant ($P < 0.05$) decrease in the accumulation of proteins in the 5 mm segment of nerve immediately proximal to the ligature was found after treatment of the nerve trunks with chloroquine and hydroxychloroquine at a concentration of 10^{-3} M and with thioridazine, clioquinol and chlorpromazine

at 10^{-4} M. Ethambutol (10^{-3} M) had no significant effect. The decrease in accumulation with chloroquine was greater than that with hydroxychloroquine at the same concentration. Both chlorpromazine and chloroquine at 10^{-3} M in the ganglion compartment caused a significant fall in protein synthesis.

The results indicate that, with the exception of ethambutol, the drugs have an inhibitory effect on the axonal transport of proteins *in vitro*. The extent to which this contributes to their retinotoxic action is unclear. Retinal RNA and protein biosynthesis are also affected by chloroquine *in vitro* at the same concentration (Giuffrida, Sjöstrand, Cambria, Serra, Vanella, Avitabile, Jarlstedt & Karlsson, 1975).

A study *in vivo* was also undertaken in which albino and pigmented rabbits were fed chloroquine diphosphate (100 mg/kg) three days per week for 6–8 months. Vagus nerves were then removed and the axonal transport of labelled proteins examined *in vitro* by the above method. No significant difference was found between control and drug-treated animals. These results with chloroquine are consistent with previous work which indicated a lack of effect of the drug on RNA and protein synthesis *in vivo* (Karlsson, Giuffrida, Jarlstedt, Serra & Sjöstrand, 1976).

Drugs were donated by: Bayer (chloroquine); Winthrop (hydroxychloroquine); Sandoz (thioridazine); Ciba-Geigy (clioquinol); Leo (chlorpromazine) and Lederle (ethambutol).

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An examination of the action of tetrabenazine on peripheral noradrenergic neurones

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Tetrabenazine has been used recently in the treatment of various forms of chorea (McLellan, Chalmers & Johnson, 1974). Its action resembles that of reserpine, but it is less potent and shorter-acting (Quinn, Shore & Brodie, 1959). The present study has examined these differences, comparing the actions of tetrabenazine and reserpine on peripheral noradrenergic neurones of rats (male Wistar; weight range 200–220 g).

Tetrabenazine (100 mg/kg i.p.) markedly decreased catecholamine induced histofluorescence in the iris, mesenteric arterioles and hepatic portal vein. Depletion was maximal 4 h after injection and fluorescence intensity returned to normal 24 h after injection. Reserpine (0.5 mg/kg i.p.) produced a similar loss of histofluorescence from the same tissues but this effect was not maximal until 18 h after injection and histofluorescence was still sub-normal 4 days after injection.

Amine-depleted irides, venae cavae and mesenteries removed from rats ($n=5$ for each drug) either 4 h after tetrabenazine treatment (100 mg/kg) or 18 h after reserpine treatment (0.5 mg/kg), were incubated with noradrenaline (5×10^{-6} M) in Krebs' solution at 37°C for 15 minutes. After washing in Krebs' solution to remove unbound noradrenaline they were incubated with 2% glyoxylic acid (buffered at pH 7) and prepared for fluorescence microscopy. Tissues from tetrabenazine-treated rats contained noradrenergic nerve terminals which had been markedly repleted by incubation with noradrenaline. Those from the reserpine-treated rats showed no restitution of fluorescence after noradrenaline-treatment. Fluorescence was restored to reserpine-treated tissues if tranylcypromine (3×10^{-5} M) was included with noradrenaline in the incubation.

Ultrastructural studies supported these findings. Noradrenaline restored electron density to synaptic vesicles in nerve terminals of the iris from