ergotoxine, a mixture of the alkaloids ergocornine and ergocryptine, obtained from different biosynthetic experiments with the same labeled precursor, which were done under as near identical conditions as possible. In the degradation of such alkaloid mixtures, a radioactivity balance usually cannot be established. The percentage distribution of radioactivity can, however, be calculated if the identical moieties in the alkaloids have the same specific radioactivities.

The procedure described here has been used routinely for the degradation of labeled ergotamine and ergotoxine samples from biosynthetic experiments. It has been found to be reliable and easy to carry out. It requires only small quantities of material, and the amount of time needed is reasonable. One complete degradation requires about 3–4 days, but the working time per sample can be reduced considerably by degrading several samples simultaneously. Although this has not been done, the degradation procedure can undoubtedly be applied to other cyclol-type peptide ergot alkaloids.

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COMMUNICATIONS

Evaluation of Cryogenine in Rat Sympathetic Ganglia

Keyphrases ☐ Cryogenine—ganglionic activity, rats ☐ Ganglionic activity—cryogenine effect, rats

Sir:

Previous reports indicated that the various pharmacologic actions ascribed to the plant extracts of *Heimia salicifolia* Link and Otto essentially are elicited by its major alkaloidal constituent, cryogenine (1–3). Recent studies demonstrated that orally administered cryogenine is equipotent to phenylbutazone in both acute and chronic models of inflammation at doses appearing to be unrelated to any systemic toxic manifestation (3). In extensive gross observational studies by Robichaud *et al.* (1), the production of mydriasis, mucosal blanching, and pilomotor erection as well as decreased motor activity were noted in rats in response to intraperitoneal administration of cryogenine.

In addition to producing mild hypothermia at relatively low, nonataxic dosage levels, cryogenine has been shown to suppress conditioned behavior responses selectively in both discrete and continuous avoidance–escape situations (4). Moreover, cardiovascular studies in the anesthetized intact dog and cat have demonstrated a significant blockade of the pressor response to exogenous epinephrine, with doses of cryogenine having no apparent effect on resting blood pressure (2, 5). Kinetic experiments on various isolated tissue preparations have demonstrated, however, an apparent lack of specificity for the commonly employed cholinergic and adrenergic receptor systems (3, 5, 6). In view of the foregoing, it was of interest to determine whether the anti-inflammatory properties attributed to cryogenine might be mediated through alterations in ganglionic activity.

Young Charles River Wistar rats of either sex were anesthetized with a mixture[1] of allobarbital (100 mg./kg.), urethan (400 mg./kg.), and monoethylurea (400 mg./kg.) administered intraperitoneally. The surgical and recording procedures employed in this superior cervical ganglion preparation were described in detail by Hancock and his coworkers (7, 8). Unless indicated otherwise, the sympathetic trunk was stimulated at a rate of 0.3 Hz. (0.2 msec.). Ganglionic potentials evoked by drugs or preganglionic stimulation were recorded from the surface of the ganglion by means of silver–silver chloride bipolar electrodes. All drugs were administered by close intraarterial injection through a 27-gauge needle inserted into the common carotid artery. The constant volume of injection was 0.05 ml., and all drugs were dissolved in a solution of 0.9% NaCl. With the exception of cryogenine (used as the acetate),

[1] Dial with Urethane, Ciba.

all dosages in the following text refer to the salt form of the drugs. Clotting in the needle was prevented by the prior administration of heparin (400 units/kg. intraarterially).

Cryogenine was administered intraarterially during continuous preganglionic stimulation at frequencies ranging from 0.1–1.0 Hz. Following injection of the drug, ganglionic transmission was monitored continuously for 2 hr. Cryogenine (50–750 mcg.) failed to produce any detectable changes in either spike amplitude or afterpotential contour evoked by supramaximal or submaximal preganglionic stimulation. The submaximal stimulation was determined by selecting the voltage that would produce a ganglionic spike one-half the amplitude of that obtained with supramaximal preganglionic stimulation. It was determined that cryogenine (50–750 mcg.) did not evoke ganglionic firing. Moreover, no changes in the resting demarcation potential were observed as the result of cryogenine administration. Similarly, there was no evidence of asynchronous postganglionic discharge evoked by cryogenine (750 mcg.) in ganglia conditioned by repetitive supramaximal preganglionic stimulation (30 Hz. for 30 sec.) or in ganglia pretreated with *d,l*-isoproterenol HCl (2 mcg.).

Ganglionic discharges evoked by acetylcholine Cl (10 mcg.), 1,1-dimethyl-4-phenylpiperazinium iodide (5 mcg.), serotonin creatinine sulfate (10 mcg.), or KCl (500 mcg.) were unaffected by cryogenine (750 mcg.) administered 5 or 60 sec. earlier.

The postganglionic firing evoked by the intraarterial administration of tetramethylammonium Cl (5–10 mcg.) was not modified in ganglia pretreated with cryogenine 15 sec. earlier. Furthermore, the biphasic ganglionic demarcation potential produced by tetramethylammonium Cl (10 mcg.) and 1,1-dimethyl-4-phenylpiperazinium iodide (5 mcg.) was unaltered by the previous administration of cryogenine (750 mcg.). The postganglionic firing produced in response to physostigmine salicylate (200 mcg.), oxotremorine picrolonate (75 mcg.), and 4-(*m*-chlorophenylcarbamoyloxy)-2-butynyltrimethylammonium Cl (25 mcg.) was unaffected by the administration of cryogenine (750 mcg.) prior to or during the evoked asynchronous discharges. Moreover, there were no apparent alterations in the enhanced level of firing evoked by these agents in ganglia pretreated with *d,l*-isoproterenol HCl (2 mcg.) or in ganglia conditioned previously by repetitive supramaximal preganglionic stimulation (30 Hz. for 30 sec.). Cryogenine (750 mcg.) failed to prevent the complete abolition of the "muscarinic" firing that occurred almost immediately following the administration of atropine sulfate (2 mcg.).

In ganglia pretreated with cryogenine immediately prior to or 30 sec. before injection of 1,1-dimethyl-4-phenylpiperazinium iodide (5 mcg.), tetramethylammonium Cl (10 mcg.), levarterenol bitartrate (0.5 mcg.), epinephrine bitartrate (0.5 mcg.), or methacholine Cl (50 mcg.), no observable antagonism or enhancement of the ganglionic blockade produced by these compounds was noted.

The lupine alkaloids (cytisine, sparteine, *etc.*) are reputed to possess a nicotinelike common denominator pharmacologically and some structural similarities with possible metabolic degradation products of cryogenine. Previous studies demonstrated, however, distinct differences between the two groups in regard to cardiovascular, anti-inflammatory, and psychopharmacologic activity (2–4, 9). The present study showed cryogenine to be devoid of any ganglionic activity at the relatively high dose levels employed. Numerous nonsteroidal anti-inflammatory drugs presently in clinical use inhibit vasoconstriction produced by a variety of vasoactive agents (10). While the anti-inflammatory efficacy of cryogenine does not appear to be related to gangliotropic activity, its actions might still be explained by interference with inflammatory mediators or tissue reactions at the neurovascular or cellular level.

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Urinary Excretion of Chlorpromazine and Chlorpromazine Sulfoxide in Four Patients on Different Days

Keyphrases ☐ Chlorpromazine and sulfoxide—urinary excretion, human ☐ Urinary excretion, chlorpromazine—daily variations

Sir:

Urinary concentrations of chlorpromazine in individuals receiving this drug were determined (1–3). The results showed wide variations among the persons tested, in spite of the fact that the same dose was administered. However, the data do not indicate whether a patient excreting low quantities of the drug on the day of