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FINAL REPORT ON NASA-GRANT NSG-346

In the original grant application the proposed research objectives were divided into three general areas:

1. Determination of areas of localization of thiethylperazine in mammalian cerebellum and associated areas.
2. Drug binding to the subcellular elements of cerebellar areas.
3. Site of action of thiethylperazine in humans and animals.

The first objective was realized completely. The results have been published and reprints accompany this report. Briefly, the results illustrate that the anti-emetic phenothiazine, thiethylperazine, has a spectrum of localization within dog brain quite different from those of tranquilizer phenothiazine, chlorpromazine and prochlorperazine. Thiethylperazine localizes primarily in vermis, paraflocculus, cerebellar cortex and fastigial nucleus of the cerebellum and restiform body and area of vestibular nuclei. This pattern of localization delineates, meaningfully or not, a cerebello-vestibular nervous pathway. This study laid the groundwork for the studies to follow attempting to correlate sites of localization with sites of action.

The overall plan to correlate these sites was to produce lesions in the areas of drug concentration and to determine whether the drug retained its anti-nystagmic and anti-emetic actions. For these studies cats, dogs and humans were employed. At the time that the cats were studied, the best means available for quantitating drug effects was by rating (0-4+) nystagmus and body attitude before and after drug and before and after surgery. This proved extremely inaccurate and clumsy. However, these early efforts stimulated the development of methods for electronic recording of nystagmus. In the human studies were included six patients with cerebellar degeneration as well as a normal population and a population of patients with vestibular problems. Nystagmus and subjective dizziness was produced in the normals and patients with cerebellar lesions before and after drug and placebo administration. Duration of nystagmus and subjective dizziness was recorded before and after drug and placebo. The normal patients as well as those with vestibular problems

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responded very well to thiethylperazine with a reduction in duration and severity of dizziness and nystagmus. The cerebellar degeneration patients on the other hand received significantly much less protection (4/6 showing no protection).

In the dogs as well, cerebellectomy severely attenuated the anti-nystagmic action of thiethylperazine.

A colony of swing-sickness susceptible dogs was selected and the protective effect of thiethylperazine noted. Attempts at producing lesions in discrete areas of these animals cerebelli and associated areas were made, but primarily because of variation in animal head size and shape the lesions could not be predictably placed. After 18 months of trying this project was abandoned.

The subcellular distribution problem was like-wise abandoned when it was realized that redistribution of drug among the various subcellular fractions could easily occur during homogenization and centrifugation. No apparent means to control for redistribution was at hand.

In brief summary, the successful research demonstrated:

1. That thiethylperazine localizes differently from tranquilizer phenothiazines.
2. That the major brain area of highest concentration in dog and rabbit is the cerebellum and areas associated with vestibular function.
3. That thiethylperazine exerts its antinystagmic action in dogs and humans, antivertigo action in humans and antiswing-sickness actions in dogs.
4. That the cerebellum needs to be intact for thiethylperazine to produce its anti-nystagmic action.

Thus an approach to correlating sites of action and localization has been made which has been partially successful.

~~Attaches~~ are reprints of two publications and a senior medical thesis resulting from this work.