EFFECT OF NUCLEUS CIRCULARIS AND LATERAL PREOPTIC LESIONS ON OSMOTICALLY INDUCED DRINKING

THESIS

Presented to the Graduate Council of the
North Texas State University in Partial
Fulfillment of the Requirements

For the Degree of

MASTER OF SCIENCE

By

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August, 1982

Wallace, Forrest, L., Effect of Nucleus Circularis and Lateral Preoptic Lesions on Osmotically Induced Drinking. Master of Science (Experimental Psychology), August, 1982, 25 pp., 3 tables, 2 illustrations, bibliography, 30 titles.

The area most widely associated with osmoreception has been the lateral preoptic nucleus. However, Hatton (1976) proposed that the nucleus circularis could be the actual osmoreceptor in the hypothalamus. The present study supported Hatton by using 30 rats which were randomly assigned to sham, lateral preoptic, and nucleus circularis lesion groups. After a 2-week post-operative period, half of each group was injected with isotonic saline while the other half was injected with hypertonic saline. Water consumption was measured at 10-minute intervals for one hour. Following a 4-day recovery period, the injection procedure was reversed. Analysis of difference scores, computed by subtracting the amount of water consumed after isotonic injection from the amount of water consumed after hypertonic injection, revealed a significant difference between the nucleus circularis group and the other two groups.

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EFFECT OF NUCLEUS CIRCULARIS AND LATERAL PREOPTIC LESIONS ON OSMOTICALLY INDUCED DRINKING

Thirst has been defined as an imbalance in body water which creates a state of excitement in the central nervous system (or disinhibits an inhibitory state) resulting in the seeking and ingestion of water (Epstein, Kissileff & Stellar, 1973). Thirst-motivated behavior and the accompanying release of an antidiuretic hormone by the posterior pituitary gland can be produced by two fluidic conditions (c.f. Verney, 1947) which, while monitored by independent mechanisms, act in an additive fashion (Oatley, 1964; Corbit, 1968). These conditions are hypovolaemia, the loss of extracellular fluid, and cellur dehydration, the loss of intracellular fluid (Gilman, 1937; Fitzsimons, 1961). The literature reviewed below will concentrate on research investigating the neural mechanisms mediating thirst-motivated behavior produced by cellular dehydration.

Cellular dehydration occurs as a result of an imbalance in osmotic gradients between intracellular and extracellular fluids. Thirst, motivated by cellular dehydration, has been called osmotic thirst (Gilman, 1937) and research in this area has been directed at locating osmoreceptors in the brain (Verney, 1947). The two areas most often implicated in osmotic thirst have been the preoptic nucleus and

the lateral hypothalamus (Epstein, Kissileff & Stellar, 1973). For example, Blass and Epstein (1971) lesioned the anteriomedial portion of the lateral preoptic nucleus and found that drinking in response to cellular dehydration produced by interperitoneal injection of hypertonic saline was abolished or substantially reduced in rats. Rehydration of the lateral preoptic nucleus via injections of distilled water by intracranial cannulation also attenuated drinking due to cellular dehydration. Using rabbits as subjects, Peck and Novin (1971) also lesioned the lateral preoptic nucleus and obtained similar results. Employing multiple and single unit recording electrodes, Malmo and Mundl (1975) measured neural activity in the medial and lateral preoptic areas after an osmotic challenge. They concluded that Blass and Epstein (1971) were correct in labelling the lateral preoptic nucleus as being osmosenstive. Almli, Golden, and McMullen (1976) lesioned the preoptic area of 10-day-old male and female rats and concluded that, as adults, the rats were hyperdispic in response to extracellular dehydration and hypodispic to cellular dehydration, which led to their support of the idea that the lateral preoptic nucleus contains osmoreceptors.

The lateral hypothalamus, occassionally in conjunction with the lateral preoptic nucleus, has also been thought to affect osmotic thirst. By alternately lesioning and recording the lateral preoptic and the lateral hypothalmus

areas, Tondat and Almli (1976) produced data which indicated that the two areas were independently osmosensitive but probably influenced one another. The data implicating the lateral hypothalamus in drinking behavior is considerable (Fitzsimons, 1979) and adipsia is a well-documented characteristic of the lateral hypothalamic syndrome, a characteristic so strong that unless the animal is force-fed water, it will die. Kissileff and Epstein (1969) also lesioned the lateral hypothalamus and, after recovery, found that drinking occured; however, this was entirely prandial (when a small amount of water is taken with each morsel of food).

There are however, some alternative interpretations of the data implicating the lateral preoptic nucleus and the lateral hypothalamus in osmotic thirst. In the studies cited above most, if not all, of the lateral preoptic lesions extended from the anterior preoptic area caudally to the anterior and lateral hypothalamus, thus destroying several surrounding areas. In addition, Peck and Novin (1971) note that their lesions of the lateral preoptic nucleus which were effective, destroyed more tissue than might be thought to be necessary and that lesions which were restricted to the area of the lateral preoptic nucleus rostral to the anterior commissure failed to produce an effect. Coburn and Stricker (1978) put forth the notion that the effects seen following lateral preoptic lesions

could possibly have been due to damage to several monoaminergic pathways which traverse the lateral preoptic area. Direct injections of hypertonic saline into the lateral preoptic area were effective only at osmotic concentrations considerably above the normal ranges of physiological osmolarity, allowing for the possibility that the saline could affect structures other than lateral preoptic nucleus due to seepage, particularly via the third ventricle (Peck & Novin, 1971).

The data which postulates that the lateral preoptic nucleus, the lateral hypothalamus or combination of the two areas control osmotic thirst by possessing osmoreceptors or osmosensitive neurons appears to be contradictory to the classic work of Verney (1947) who postulated that osmoreceptors existed in the central nervous system and were probably located in the vascular bed supplying the supraoptic nucleus. The osmoreceptive cells were thought to mediate release of an antidiuretic hormone (ADH) and osmotic thirst by acting on the supraoptic nucleus as well as directly communicating with the posterior pituitary. Evidence has since been presented that the supraoptic nucleus does have a direct connection with the releases of ADH (Zuidema & Clark, 1957). Shafer (c.f. Verney, 1947), in 1909, provided the vital link between the pituitary and the kidneys via an antidiuretic product thus completing the chain from a neural control mechanism to urine output.

Verney's (1947) prediction about the possible location of a neural osmoreceptor has been strongly supported by research on a relatively unknown structure, the nucleus circularis, which lies in the vascular bed supplying supraoptic nucleus (Hatton, 1976; Tweedle & Hatton, 1976; Lambert, Ivy, & Harrell, 1980). The nucleus circularis is a tightly packed grouping of approximately 260-280 cells in each bilateral area, and is located posterior to the anterior commissure, ventral to the paraventricular nucleus, and about midway between the paraventricular nucleus and the base of the brain. It also lies midway between the third ventricle and the supraoptic nucleus. Because of its small size and close proximity to the supraoptic and paraventricular nuclei, the nucleus circularis had earlier been labeled as the "accessory supraoptic nucleus" and "nucleus paraventricularis pars lateralis" (Peterson, 1966). Monachov, Boon, and Brockhaus list this small group of cells as the nucleus intermedius, while Diepen designated "intermediate Zellnester" as the nucleus' name (c.f. Palkovits, 1974). It was Peterson (1966), however, who named the structure as the nucleus circularis due to the nucleus' characteristic shape when seen by a frontal section.

The nuclei in this area of the hypothalamus originate from a common phylogenetic source, an area which lies adjacent to the epydymal lining of the lateral wall of the third ventricle. The paraventricular nucleus remained

relatively close to its site of origin while the intermediary nuclei and the supraoptic nucleus have migrated ventrolaterally towards the outer border of the optic chiasm. The nucleus circularis is, therefore, phylogenetically older than the supraoptic nucleus but younger than the paraventricular nuclues (Bandaranayake, 1971). Because of the proximity and common origin of the three nuclear groups, the nucleus circularis has been associated with the supraoptic and the paraventricular nuclei, both of which secrete ADH.

The nucleus circularis is determined to be neuroscretory based on the presence of Gomori-stainable material, nematosomes, in the cytoplasm (Peterson, 1966). Tweddle and Hatton (1976) also noted processes near and enamating from the some of cells in the nucleus circularis which contained ribosomes and neurosecretory granules as well as synapses. The majority of these cells seem to be monopolar with unmyelinated axons. In addition, some of the cells seem to be perforated by capillaries from the bed in which the nucleus lies. A myelin capsule encases the entire nucleus (Hatton, 1976). Peterson (1966) found that the nucleus has a tubular shape with axons running down its center and is usually associated with a large blood vessel. Some axons project toward the supraoptic nucleus while others join axons from the paraventricular nucleus and project toward the neurohypophysis (Bandaranayake, 1971; Koizumi, 1964;

Laqueur, 1954). When horseradish peroxidase, a substance which is transported up the axon in a retrograde fashion and leaves a reaction product thereby making it possible to trace an axon to its nuclues, was injected into the pituitary of a rat, it was found that some neurosecretory axons led directly to the nucleus circularis (Sherlock, Field, & Raisman, 1975). The cells of the nucleus are also responsive to osmotic changes, such as those produced by water deprivation (Tweedle & Hatton, 1976, 1980; Gregory, Tweedle, & Hatton, 1980; Hatton & Walters, 1973). These characteristics led to the hypothesis that the nucleus circularis may perform a sensory function as an osmoreceptor, receiving input from the capillary blood perfusing it via osmolarity variations (Hatton, 1976), much as Verney (1947) had predicted.

Two recent studies have outlined the structural changes in the nucleus circularis which take place after dehydration. The first to actually examine the nucleus circularis was Hatton (1976) who found that the percentage of cells containing multiple nucleoli increased from 10% to 28% with only 24 hours of water deprivation (cellular dehydration). Unilateral electrical stimulation of the nucleus circularis produced a decrease in urine output intimating the direct, or at least indirect, control of ADH secretion. The second study showed that water deprivation also produced enlarged nucleoli as well as an increase in free ribosomes and rough endoplasmic reticulum. Another characteristic which

increased was the percentage of direct intercellular contact, thus implying increased generator potential and synchronization of firing for the cell group as a whole. An additional change observed after dehydration was an increase in the percentage of marginated nuclei (Tweedle & Hatton, 1976). The nucleus circularis did fulfill six out of Hatton's seven criteria for classification as an osmoreceptor, while the seventh (results from intracellular recording) has not been tested as yet. However, no documented study attempted to analyze drinking behavior following an osmotic challenge with animals subjected to discrete lesions of the nucleus circularis until the work by Lambert, Ivy and Harrell (1980).

The only research to examine the behavioral effects of small, localized lesions of the nucleus circularis following an osmotic challenge was by Lambert, Ivy, and Harrell (1980). By using lesion parameters of 1-ma anodal current for one second the lesions were restricted to the area of the nucleus circularis and did not encroach on the preoptic, paraventricular or supraopatic. Also, no lesion extended forward beyond the anterior commissure. Lambert, Ivy, and Harrell (1980) point out that bilateral destruction of the nucleus circularis was not necessary to produce the dramatic results they obtained. It is possible that their lesions disrupted fiber pathways between the nucleus circularis and either the supraoptic nucleus, the paraventricular nucleus or the pituitary or a combination of these nuclei. Yet a

significant difference was found between the nucleus circularis lesioned group and the sham-operant group.

The results of Lambert, Ivy, and Harrell (1980) have yet to be replicated and given that such noticable behavioral effects are not usually observed with such small lesions, replication is warranted. Also no previous study has shown a deficit in osmotic thirst using small lesions restricted to the lateral preoptic nucleus. Therefore, the purpose of the present study was to replicate Lambert, Ivy, and Harrell (1980) and to observe the effect of small lesions of the lateral preoptic nucleus on osmotic thirst. It was hypothesized that a group of rats with lesions of the nucleus circularis would drink less water in response to an osmotic challenge than a lateral preoptic lesioned group and a sham-operant group.

Method

Subjects

The subjects were 30 albino, male Sprague-Dawley rats whose weight at the time of surgery was approximately 350 grams. The animals were individually housed and had ad libitum access to food and water until two hours before testing when both food and water were removed.

Surgical Procedure

Anesthesia was accomplished by intraperitoneal injection of 50 mg/kg of Nembutal. Post-surgery respitory edema was controlled using .33 cc of atropine. Bilateral lesions were

produced using a 1-ma anodal, anally grounded direct current for two seconds. Coordinates for lateral preoptic nucleus lesions were 9.0 mm anterior to the intrauural plane; 7.3 mm below the surface of the dura mater; and 1.5 mm lateral to the center of the sagital sinus. Lesions in nucleus circularis animals were placed 1.8 mm posterior to bregma; 1.9 mm lateral to the center of the sagital sinus; and 7.5 mm below the surface of the dura mater. The sham-operant group received the same treatment as the nucleus circularis group except that the electrode was lowered to a point 1 mm above the area of the nucleus circularis and no current was passed.

Histology

The animals were sacrificed with an overdose of ether and were perfused intracardially with normal saline followed by 10% Formalin. The brains were embedded in Parlodion, microtomed in frontal sections with a thickness of approximately 30 microns per section, stained with Thionin and mounted on individual slides.

Testing Procedure

An acclimatization period of one week before surgery and a recovery period of two weeks after surgery were implemented. The animals were tested on two days with a four-day interval separating the tests. All subjects were divided into two groups; one received hypertonic saline (.75 M NaCl) and the other received isotonic saline. Animals which received hypertonic saline on Day one received isotonic saline on Day two.

The two test groups were counterbalanced for experimental group, the position of the cage in the housing rack and positional order of injection. Diurnal cycling was controlled by giving the injections during the same time period on both test days, even though Oatley (1967) has shown that the time of day does not appear to affect drinking in response to an osmotic challenge.

Cellular dehydration was induced by interperitoneal injection of hypertonic saline using a 5 cc Lure lock syringe with a 27 guage, .5-inch needle. Isotonic saline was injected to control for the effect of the injection and the weight of the saline. The amount of saline injected was 1% of each animal's body weight. This method contolled for variation in subject size. Thirst was operationally defined as the volume of water consumed during a one hour period beginning immediately after the injection. Water consumption was measured in six 10-minute intervals using drinking tubes which were graduated to .1 ml and placed on the animal's home cage. All food and water were removed two hours prior to testing.

Results

Difference scores were computed by subtracting the amount of water consumed after isotonic injection from the amount of water consumed after hypertonic injection for each animal in each 10-minute period (non-cumulative) and by subtracting the amount consumed up to each 10-minute period

(cumulative). Based on histological results, one animal in the nucleus circularis lesioned group was eliminated from the data analysis. This subject's lesions were in the posterior hypothalamus while all other animals in this group had lesions in the area of the nuclues circularis. Histology also showed that no nucleus circularis lesion extended forward past the anterior commissure. All animals in the lateral preoptic group had lesions which were within the borders of the lateral preoptic nucleus. A 3 x 6 analysis of variance with one repeated measure was performed on both cumulative and non-cumulative data. Analysis of cumulative data showed a significant interaction of experimental group and measurement interval ($p < .02$, $F = 2.43345$, $df = 10,130$), as well as a significant main effect of measurement interval ($p < .001$, $F = 71.55599$, $df = 5,130$). Post hoc tests showed a difference between intervals 4, 5 and 6 with the other intervals but not with each other. A summary table of this analysis is provided in Table 1, and a graph of the cell means can be found in Appendix A. Analysis of non-cumulative data showed significant main effects for experimental groups ($p < .04$, $F = 3.92553$, $df = 2,26$), with the nucleus circularis group being different from the lateral preoptic nucleus and sham-operant groups while the latter two did not differ significantly from each other, and for measurement intervals ($p < .001$, $F = 12.29427$, $df = 5,130$), with intervals 2 and 3 being different from the other intervals but not different

from each other. A summary table of this analysis is provided in Table 2 and a graph of the cell means can be found in Appendix B.

Table 1

Summary Table for Cumulative Data

Source	SS	DF	MS	F	P
A	481.77	5	96.34	71.56	.142
B	97.89	2	48.95	2.11	.001
AB	32.77	10	3.28	2.43	.011

Table 2

Summary Table for Non-Cumulative Data

Source	SS	DF	MS	F	P
A	83.82	5	16.76	12.29	.032
B	6.91	2	3.46	3.93	.001
AB	11.74	10	1.17	0.82	.572

Discussion

The basic hypothesis of this study was that rats with small lesions in the area of the nucleus circularis would consume less water in a one hour period than rats with small lesions in the lateral preoptic nucleus of sham-operant animals following interperitoneal injections of hypertonic

saline. This hypothesis was supported. In addition, it was found that rats with small lesions in the lateral preoptic nucleus did not differ significantly from the sham-operant group and were, in fact, behaviorally indistinguishable from the sham-operants. The sham-operant group in the present study responded with a magnitude which was equivalent to the sham-operant animals employed by Lambert, Ivy, and Harrell (1980) thus providing consistency of controls between the current study and the only prior research to take behavioral measures of the influence of the nucleus circularis on osmotic thirst. Results from the present study lend strong support to Verney's (1947) conclusion that osmoreceptors are located in the vascular bed supplying the supraoptic nucleus and to Hatton's (1976) proposal that the nucleus circularis could be just such an osmoreceptor. However, data from the present study does not support the contention that the lateral preoptic nucleus is an osmoreceptor and seems to indicate that the lateral preoptic nucleus may not serve as a receptor.

These results raise questions about the true role of the lateral preoptic nucleus in the regulation of osmotic thirst. These questions were noted by Hatton (1976) who stated that the effects of lesions in the lateral preoptic nucleus are to disrupt drinking behavior rather than initiate such behavior as one would expect when a receptor is damaged. One possible explanation for the discrepancy between earlier

studies which proclaimed that the lateral preoptic nucleus was an osmoreceptor and the present study is that the nucleus circularis could control short-term, immediate osmotic thirst imbalances while the lateral preoptic nucleus governs the long-term, homeostatic mechanisms. This conjecture is based on Hatton's (1976) report that the effects of stimulation in the area of the nucleus circularis lasted approximately 20 minutes after the stimulation ceased, and studies which stimulated the lateral preoptic nucleus reporting effects that lasted somewhat longer, in some cases hours longer (Peck & Novin, 1971; Blass & Epstein, 1971). A second possible explanation is that the lesions in the present study were too small to affect the lateral preoptic nucleus if the stucture is diffuse and requires ablation of the entire nucleus to produce the deficit. Peck and Novin (1971) agree that large lesions of the lateral preoptic nucleus are necessary to obviate behavioral responses to an osmotic challenge and offer this proposal as an explanation for the lack of deficit in their animals with lesions restricted to the lateral preoptic nucleus.

A third alternative is that the studies which lesioned the lateral preoptic nucleus also damaged either the nucleus circularis or related fiber pathways. Lesions by Lambert, Ivy, and Harrell (1980) and the present study did not bilaterally destroy the nucleus circularis but did produce deficits in drinking behavior. This suggests that prior

studies reporting the lateral preoptic nucleus as an osmoreceptor (Blass & Epstein, 1971; Peck & Novin, 1971; Coburn & Stricker, 1978) were actually damaging the nucleus circularis or fiber tracts to and from the nucleus circularis since most of these works employed lesions which often extended from the anterior portion of the lateral preoptic nucleus to the area of the nucleus circularis. Thus even if the nucleus circularis was left intact, its fiber tracts could be injured, producing the behavioral effects attributed to the lateral preoptic nucleus. The present study lends support to the surmise that the lateral preoptic nucleus may not be an osmoreceptor because animals with lesions restricted to the lateral preoptic nucleus responded in a fashion which was almost indistinguishable from sham-operant animals.

Future research is in order to determine if any of these alternatives are valid. Animals with nucleus circularis lesions could be tested for recovery effect, much in the same fashion as the lateral hypothalmic syndrome. One group of animals with lesions in the nucleus circularis could be water deprived than tested against another group of nucleus circularis lesioned animals to test for a deficit in drinking behavior without using an osmotic challenge. According to Hatton (1976), four hour deprivation should be sufficient. While measuring the effects of stimulation on the nucules circularis, Hatton (1976) obtained significant results using unilateral stimulation. This raises questions regarding the

necessity of bilateral damage to produce a behavioral deficit to an osmotic challenge. Additional research is required to determine if unilateral damage is sufficient to produce behavioral effects equivalent to those found in the present study and the work by Lambert, Ivy, and Harrell (1980). A study suggested by Hatton (1976) is intracellular recording from the nucleus circularis before, during and after cellular dehydration. It would also be advantageous to determine whether the nucleus circularis cells secrete ADH, a precursor to ADH or some related hormone. Because of the location of the nucleus circularis in the anterior hypothalamus, which is instrumental in regulating biological cycles, lesions of this area may alter or disrupt cyclic drinking, therefore further study is needed to establish what, if any, effects on cycles are produced by these lesions. The current study and Lambert, Ivy, and Harrell (1980) used males to control for as much biological cyling as possible but additional research is in order to determine if females show the same deficit to an osmotic challenge as males.

In summary, the present study offered a brief overview of thirst due to cellular hydration with special consideration given to the lateral preoptic nucleus and a relatively little known structure, the nucleus circularis, and examined the effects of discrete lesions in the lateral preoptic nucleus and the area of the nucleus circularis in rats using sham-operant animals as controls. While the lateral preoptic

nucleus lesioned group responded in a manner virtually identical to the sham-operant gorup, the nucleus circularis lesioned group showed a pronouced deficit in drinking behavior following an osmotic challenge. These results lend strong support to Verney's (1947) surmise that osmoreceptors could be located in the vasuclar bed supplying the supraoptic nucleus and Hatton's (1976) contention that the nucleus circularis might be that osmoreceptor. In addition, questions have been raised as to the true role of the lateral preoptic nuclues in osmoreception. Subsequent research in this area should decide these questions.

Appendix A

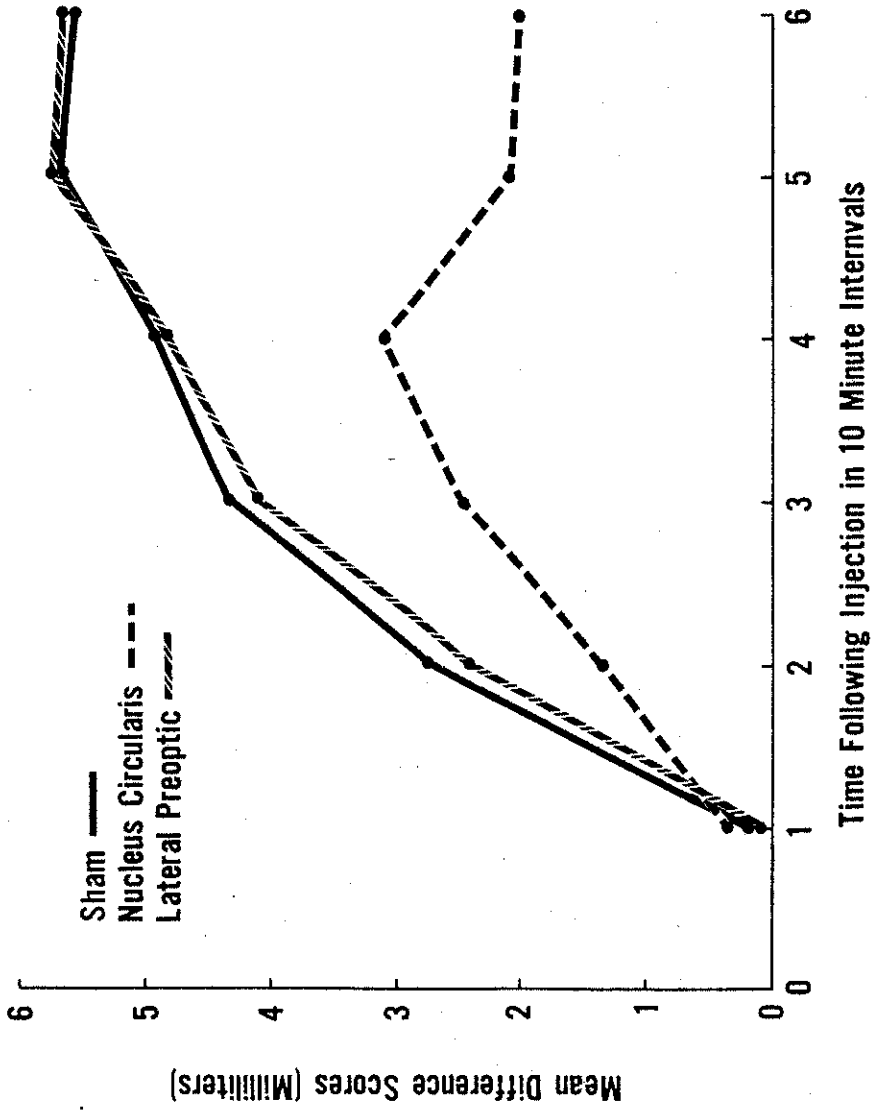

Figure 1. Cumulative mean difference scores in milliliters versus a function of the time following injection.

Appendix B

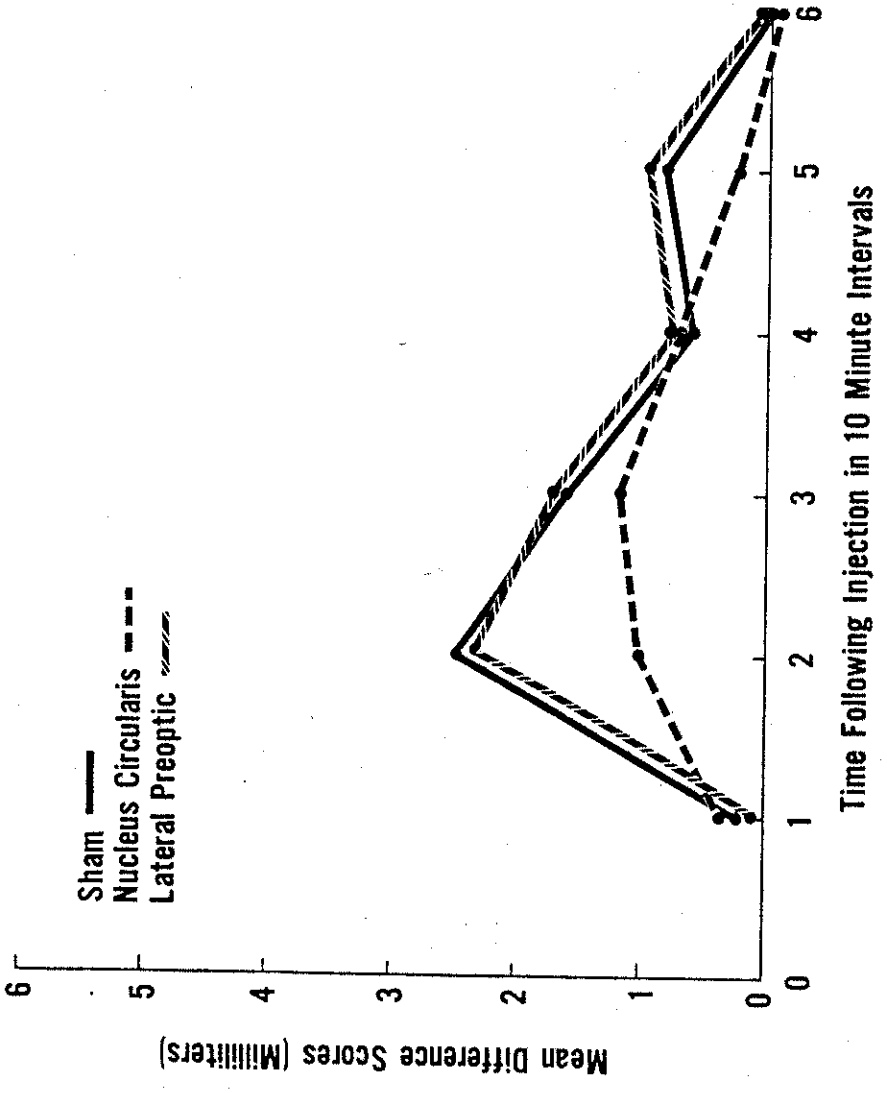

Figure 2. Non-cumulative mean difference scores in milliliters versus a function of the time following injection.

Appendix C

Table 3

Mean and Standard Deviations for Cumulative and Non-Cumulative Data

	Test Period					
	1	2	3	4	5	6
NC	.33	1.00	1.11	.67	.11	-.11
LPON	.10	2.30	1.70	.70	.90	0.00
SHAM	.20	2.50	1.60	.60	.80	-.10
	Non-Cumulative (Means)					
NC	.50	1.22	1.36	.71	.60	.33
LPON	1.10	1.89	1.34	1.25	.99	.67
SHAM	.79	2.17	1.26	1.26	.63	.57
	Non-Cumulative (S. D.)					
NC	.33	1.33	2.44	3.11	3.22	3.11
LPON	.10	2.40	4.10	4.80	5.70	5.70
SHAM	.20	2.70	4.30	4.90	5.70	5.60
	Cumulative (Means)					
NC	.50	1.32	1.42	1.27	1.56	1.54
LPON	1.10	2.46	3.04	2.49	2.21	1.95
SHAM	.79	2.50	2.80	3.35	3.27	3.06
	Cumulative (S.D.)					

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