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THE CHRONOPHARMACOLOGY OF L-DOPA: IMPLICATIONS FOR ORTHOCHRONAL THERAPY IN THE PREVENTION OF CIRCADIAN DYSCHRONISM

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The Chronopharmacology of L-DOPA: Implications for Orthochronal Therapy in the Prevention of Circadian Dyschronism*

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INTRODUCTION

The vast majority of chronopharmacologically oriented studies reported to date have tended to focus upon such relatively gross performance measures as enhanced viability, enlarged tolerance, and diminished susceptibility to toxic agents and to drugs as a function of the circadian system phase at the time of administration of the agent of choice (Reinberg and Halberg, 1971, Moore Ede, 1973, Halberg et al., 1973, Sothern et al., 1977). Few studies have employed what we have chosen to call the orthochronal molecular approach, in which the "correct time" for administering an agent is imputed from what we know about the molecular chronotype of the organism, and in which acceptable performance ordinarily corresponds to more subtle measures, including especially the absence of dyschronogenic or of phase shifting effects. By way of example, the chronobiotic action of the methylated xanthines (Ehret et al., 1975, Mayer and Scherer, 1975) correlates directly with their temporally characteristic action on glycogen depletion and on chronotypically inducible enzymes (Ehret and Potter, 1974); if phase delay or phase advance is to be averted, then these drugs are not to be taken during either the very early or very late hours of the active phase (Ehret et al., 1977a). Similarly, catecholamine formation in the rodent brain is sensitive to food ingestion - a high protein meal increases the synthesis of catecholamines; a meal that is high in carbohydrates prevents this increase and causes an acceleration in the rate of serotonin synthesis (Fernstrom, 1976). Since high levels of norepinephrine appear chronotypically during the active phase, and of serotonin during the inactive phase of the circadian cycle (Schering et al., 1968, Sauerbier and Mayersbach, 1976, Ehret et al., 1977b), it follows that an orthochronal diet (high protein breakfast, high carbohydrate supper) ought to be superior to a heterochronal diet (high carbohydrate

breakfast, high protein supper) in avoiding dyschronogenesis under duress. Experiments on the circadian regulation of body temperature in the Rat clearly show that this is indeed the case (Ehret et al., 1977a). Further considerations of the apparently general and, at the same time, central role of the catecholamine and indoleamine metabolic pathways in circadian regulation have led to the conclusion that deleterious as well as beneficial effects ought to be expected to arise from either the heterochronal or the orthochronal circadian intervention that must be associated with the application of any one of the bourgeoning array of antihypertensive, anesthetic, and psychotropic drugs that influence these pathways. Against this background, we predicted that L-β-3,4-dihydroxyphenylalanine (L-DOPA), given in the food, would act as a chronobiotic, and under some conditions be dyschronogenic. We also chose to test it chronopharmacologically because of its importance in medicine, because of its spotty record in alleviating the symptoms of parkinsonism (Goodman and Gilman, 1975), and because of its central role in catecholamine metabolism (Duncan, 1972). The results given below describe the influence of the circadian phase time-of-administration of L-DOPA given in the food upon the circadian rhythm of whole animals, as judged by measures of core temperatures in male rats. Also tested are the animals' abilities to respond to food-induced phase shifts of 90, 180, and 270 degrees as a function of the presence or absence of L-DOPA in the food either early or late in the feeding phase.

MATERIALS AND METHODS

Male rats of the Charles River CD strain between 6 and 12 months of age were housed individually in thirty-six cylindrical glass cages, suspended on stainless steel wire grids, and visually isolated from one another by a

foil-wrapped barrier that also served as a radio-frequency shield. Deep-body temperatures of each animal were monitored by miniature radiotelemeters (LeBuis and Eisler, 1977) implanted intraperitoneally, and temperature measures were recorded on tape at 20 m intervals. Programmed feeding of the animals was accomplished by stainless steel food hoppers, two per cage, which can enter or leave the cage area on clock command by a motor switching system. This arrangement permits the splitting of the feeding phase (F) during "feed-starve" (FS) entrainment cycles into an early feeding (F_1, like "breakfast") and a later feeding (F_2, like "supper") thus allowing the administration of a chronobiotic in the diet at various times of the day. Distilled water was continuously available.

Illumination during entrainment was provided by 15 W daylight fluorescent lamps that contributed about 800 lux at cage level during L phases of light-"dark" (LD) cycles; the latter consisted of 16 h of D and 8 h of L daily (DL 16:8). During D phases cages were dimly illuminated at about 30 lux from 15 W incandescent lamps operated constantly at 70% full power. Animals were housed in controlled environment rooms maintained at 20°C and 50% R.H. The entire system for programmed feeding and data acquisition is described in detail elsewhere (Meinert et al., 1977).

Unless otherwise stated, the animals were fed a standard control diet of Wayne Lab Blox (24% protein, Wayne Laboratories). The administration of L-DOPA in the diet was accomplished by first pulverizing the control diet and then adding to it an aqueous suspension of L-DOPA (L-β-3,4-dihydroxyphenylalanine, Sigma Chemical Co.). This was then mixed, formed into sheets (approximately 13 mm in thick) and baked at 200°F for 30 min to drive off the bulk of the moisture. The final concentration of L-DOPA in the diet was 30 mg L-DOPA per g chow.

Statistical time-series analysis of temperature data was accomplished following the cosinor method of Halberg et al. (1972) and Rummel et al. (1974). Briefly, a single cosine function is applied to time-series data using the method of linear least squares. In addition, confidence regions are calculated for the mesor (M), the statistically adjusted mean of the rhythm; amplitude (A), the maximum cosine height from the mesor; and acrophase (ϕ) Halberg and Katinas (1973), the time of day when the amplitude of the cosine function is greatest. By way of example, consider Figures 1, 5, 7, and 9 which show typical longitudinal circadian chronograms of raw data of rodent intraperitoneal temperature. Using the cosinor statistical procedure, under a variety of experimental exposure conditions, average daily temperatures (mesors) remain remarkably constant (37.54 C, SE ± 0.02); whereas thermal peaks (acrophases) and excursions from the mesors (amplitudes) vary considerably; the latter measures along with their 99% confidence arcs (CA) and 99% confidence intervals (CI) are given in Figures 2, 3, 6, 8, 10, and 11.

RESULTS

The top four telemetry tracings of Figure 1 show that rats acclimatized to the presence of L-DOPA in the diet for half of each day for several days (days 12-14) retain as strong a circadian rhythm (remain as euchronic) on subsequent days as do control animals, provided that the availability of DOPA occurs late in the active phase, i.e., after the acrophase for deep-body temperature (days 15-19). It is important to note that during the first three days of FF a phase drift of about 3 h has occurred in all animals, including the controls, placing the decline from the thermal acrophase close to midnight in all cases by the start of day 15. This drift removed rats 2, 3, and 4 (from the top) from the jeopardy of L-DOPA availability during the early active phase, which had clearly begun already to take its toll

on euchronism on day 13. On the other hand, this phase drift moved rats 5, 6, and 7 into the jeopardy of L-DOPA availability in the early active phase by days 14 and 15 (cf. control example as well), and the animals became dyschronic. Finally, the continual availability of L-DOPA in the diet throughout the day (FF L-DOPA, e.g. bottom rat, Figure 1) resulted in mild to moderate dyschronism during acclimatization (e.g., d 14) but this was short lived and followed by good circadian synchronization, the example given here being the worst of the group of 9 analyzed in Figure 2.

The longitudinal data presented as chronograms of 8 rats in Figure 1 is representative of that collected from 31 rats, and is analyzed statistically in Figure 2. Group A, representative of all groups for 5 days during entrainment, shows a thermal acrophase at 1529 h, typically 6.5 h after the start of the dark phase (which, on DL 16:8, extended from 0900 h to 0100 h). The remaining groups consisted of at least 7 rats computed for the fairly stabilized five days of free run (DDFF), from day 15 to day 19. Group C, 7 rats on the control diet alone, shows that an average phase delay ($\Delta\phi^-$) in free run ("phase drift") of 3 h 10 m has occurred in these controls. Group B, consisting of 9 rats continually exposed to L-DOPA in the diet, shows a comparable $\Delta\phi^-$, this time of 3 h 8 m, with narrow CA and substantial A. Similarly, group D, consisting of 8 rats that had received L-DOPA after the thermal acrophase on days 15-19, showed a strong $\Delta\phi^-$ of 5 h 9 m (which we interpret as a selective accommodation to orthochronal uptake of L-DOPA) with narrow CA and substantial A. In striking contrast, group E, consisting of 7 rats that had received L-DOPA before the thermal acrophase showed a possible $\Delta\phi$ of 6 h 12 m (which we interpret as a possible continuing search for orthochronal uptake of L-DOPA) with a wide CA and nearly minimal A: another degree Celsius, and the CI would have overlapped the pole of the cosinor, indicative of complete dyschronism for members of the group. We should note here that had we chosen to display

in this presentation a separate cosinor for each rat, for each one of the days 15-19 (easy enough to do, but terribly laborious for the reader), then every member of the E group (save one) would have shown complete dyschronism on one or more days. On the other hand, on such terms no member of groups A-D (save the one discussed in Figure 1, bottom) could have been called dyschronic.

By the way of illustration of the dyschronogenic effect of L-DOPA, as well as by way of illustration of the powers and limits of the cosinor representation of "euchronism" and "dyschronism," we have prepared another plot of the three worst members of Group E, Figure 2 (animals 5, 6, 7 from the top, Figure 1). In this plot, shown in Figure 3, it is not surprising to see an animal like 5, here called "A," totally dyschronic - it may be rather surprising to see that animals 6 and 7 are assigned apparently significant ϕ values (with expectedly large CA's) and apparently significant though evidently small amplitudes. None the less, these are the actual values shown for such evidently (Figure 1) chronotypically disturbed specimens.

Figure 4 represents an interpretation of these results, such as would not normally appear in the "Results" section of a paper, but rather in the "Discussion." This interpretation is included here in order to make sensible the design of the experiments that follow: Most concisely, the lower half of Figure 4 reads as follows: in the presence of a control diet, animals remain euchronic; their ϕ's and A's remain definitive and predictable. If L-DOPA is given later than the thermal acrophase, then all is well, and euchronism is assured. If L-DOPA is given earlier than the thermal acrophase, then dyschronogenesis will occur. The top half of Figure 4 presents an interpretation of why this should be the case: the ingestion of L-DOPA presents a challenge to circadian euchronism only during the pre-acrophase interval, during which time a chronotypic pathway block of the further

synthesis of L-DOPA (negative feed back) is expected (Duncan 1972). Ingestion of L-DOPA later in the circadian cycle (right half) results in no chronobiological disturbance since the catecholamine pathway is alredy "turned off."

Because of these results, we predicted that an animal's capacity to respond to food-induced phase shifts would be influenced by the time of day (or better, phase of cycle) during which it happened to have available to consume, or not to consume L-DOPA in the diet. The remaining experiments in this series include tests of the ability of rats to respond to phase shifts of 90, 180, and 270 degrees under these diverse circumstances. One sort of control for the lot is given in Figure 5. In this case, no phase shift is demanded during entrainment; yet one consequence is realized: for animals which consume L-DOPA before the thermal acrophase (Group B, Figure 6) the value of A is diminished and of CI (as a percentage of A) is increased enormously. It is clearly better for a rat to have ingested its L-DOPA past the thermal acrophase (Group A), even when in the cause of merely "staying-put" chronotypically.

More striking results are given in subsequent figures that represent the responses of animals to a variety of zeitgeber commands in the form of food-timing signals to shift their circadian thermal acrophases in Figure 7, the feeding protocol anticipates a $\Delta\phi^-$ of 6 h. The best $\Delta\phi$ that is seen from a three day average of days 19, 20, and 21 is that shown by Group A, of 3 h and 48 m, Figure 8, a $\Delta\phi$ (which corresponds to DOPA in F_2, Figure 7). Runner up is Group B, with a $\Delta\phi^-$ of only 2 h and 34 m (Figure 8) and which corresponds to DOPA in F_1, Figure 7.

In Figure 9, top half, a $\Delta\phi^-$ of 12 h is demanded by the feeding protocol. The best $\Delta\phi$ that is seen from a 3 d average of days 19, 20, and 21 is that shown by Group A, Figure 10, a $\Delta\phi^-$ of 7 h 38 m (which corresponds to DOPA

in F_2, Figure 9, top). Second to this is Group B, which corresponds to DOPA in F_1, with a $\Delta\phi^-$ of only 4 h 5 m.

In Figure 9, bottom half, a $\Delta\phi^-$ of 18 h is demanded by the feeding protocol, which corresponds to a $\Delta\phi^+$ of 6 h. Careful inspection in this case of the feeding protocol shows at once that the meal termed "F_2" will be consumed during the early active phase (morelike "breakfast") and that the meal termed "F_1" will be physiologically more like "supper" to the animals involved. Once again the best $\Delta\phi$ that is seen from a 3 d average of days 20, 21, and 22 is that shown by Group A, namely these animals that were presented with L-DOPA in their diets late in their active phases, which corresponds in this exceptional case to DOPA in F_1, Figure 9, bottom. This straightforwardly represents either a successful $\Delta\phi^-$ of 15 h 5 m, or a successful $\Delta\phi^+$ of 8 h 45 m. The alternative protocol, Group B, corresponding to availability of L-DOPA only during the early active phase, resulted in complete dsychronism regarding Group A, (q.v., Figure 11, A 0.14, CI .56, and P 0.3080). At the same time, we note with caution that having achieved this large $\Delta\phi$ rapidly and successfully, any extension of the same temporal protocol without further regard for the new and now vulnerable position of the acrophase would undoubtedly result in a new round of dyschronism, arising from the ingestion of L-DOPA during early active phase (q.v., the relation of A to F_1 on Figure 11, and of F_1 to the acrophase on day 22, Figure 9, bottom).

DISCUSSION

Two series of experimental results show a significant influence of the circadian phase time-of-administration of L-DOPA upon the circadian rhythm of the rat, as judged by measures of core temperature. In the first series animals were placed in free run in constant darkness and with food continually available (DDFF), but with L-DOPA-containing chow available half of the day

and DOPA-free chow available the remaining half day. These experiments show a strong correlation between circadian dyschronism and the consumption of L-DOPA prior to the acrophase. On the other hand, animals fed L-DOPA either after the circadian acrophase or ad libitum showed little or no dyschronism. In the second series, the response to food-induced phase shifts ($\Delta\phi^-$) of 90, 180, and 270 degrees was tested, and it was seen that in every case the availability of L-DOPA early in the active phase, before the thermal acrophase, inhibits phase shift, and the availability of L-DOPA after the thermal acrophase promotes phase shift. It is interesting to note that even the controls in the second series, (those animals that were required to make no $\Delta\phi$, Figure 5), exhibited marginal dyschronism on several days in the group in which DOPA was given in F_1, before the acrophase, and that this is reflected as well in the day-group averages (Group B, Figure 6).

In all cases whenever DOPA was available, either during FF (first series) or during either F_1 or F_2 of an FS cycle (second series) significant quantities of the DOPA-containing chow were consumed. However in those groups of rats that were subjected to the greatest phase shifts in the second series, the quantities consumed were somewhat variable (Table I), yet clearly large enough to influence their circadian regulatory system.

Taken altogether, the results are consistent with the interpretation given in Figure 4: if L-DOPA is consumed early in the active phase, before the thermal acrophase, then a chronotypic block to tyrosine 3-hydroxylase prevents further synthesis of L-DOPA and shuts down this pathway (Duncan, 1974). In the normal rat, the chronotypically correct (orthochronal) phase in which to give L-DOPA with least disturbances to the circadian regulatory system coincides with the time at which synthetic activity in the catecholamine ("awake") pathway normally (chronotypically) diminishes. The circadian literature contains several other references to chronopharmacologic and

and circadian phase alteration effects from catecholamine pathway activators and inhibitors including reserpine (Anderson, 1961, Halberg, 1963, Wahlström, 1965), thiopidazine (Stroebel, 1969), and α-methyldopa (Post and Nair, 1977). It should not go unnoticed that the deleterious side effects of most of these drugs include mental depressive illness, a condition nearly invariably associated with circadian irregularities and dyschronism (Halberg, 1968, Pflug, 1976).

From the preceding, it follows that, in order to minimize the deleterious side effects and maximize the beneficial effects of a drug such as L-DOPA, orthochronal therapy is indicated. How "orthochronal" is to be defined when extrapolated to organisms apparently deficient in either tyrosine hydroxylase or in L-DOPA itself (as in the case Parkinson's disease) will require experimental trial with appropriate subjects.

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TABLE LEGEND

Table I. A record of the average food consumed per day from early (F_1) and from late (F_2) food hoppers in the course of a phase response by rats to food, and to food containing L-DOPA (30 mg/g) as zeitgebers, given either in the new F_1 or in the new F_2 phase.

text figure	zeitgeber phase shift (feeding time) $\Delta\Phi$	control (no DOPA) average food consumed/day (g)		DOPA in F_1 average food consumed/day (g)		DOPA in F_2 average food consumed/day (g)		ratio F_1/F_2 (control)	ratio F_1/F_2 (DOPA in F_1)	ratio F_1/F_2 (DOPA in F_2)
		early (F_1)	late (F_2)	early (F_1)	late (F_2)	early (F_1)	late (F_2)			
5	0° = 0 h	12.1	12.4	11.7	9.5	10.3	12.5	1/1	1.2/1	1/1.2
7	90° = -6 h	20.9	7.1	15.4	6.6	16.6	8.9	3/1	2.3/1	1.9/1
9 (top)	180° = -12 h	14.1	6.0	10.6	6.6	15.1	6.6	2.4/1	1.6/1	2.3/1
9 (bottom)	270° = -18 h (90° = +6 h)	14.4	9.6	13.5	6.9	14.0	5.7	1.5/1	2.0/1	2.5/1

FIGURE LEGENDS

Figure 1. Telemetry tracings of intraperitoneal temperatures for 8 rats measured every 20 min are shown over 14 days. During days 1 through 8 (1-5 not shown), the animals were entrained by daily programs of feeding (FS 8:16) and illumination (DL 16:8). Following 2 days starvation (SS) in continuous dim light (DD), the animals were feed ad libitum (FF) for the next 8.5 days (see top protocol bars). During day 10.5-19, the top animal was maintained as a control receiving only the standard 24% protein control diet. Animals 2, 3, and 4 from the top received a diet containing 30 mg L-DOPA/g chow (other dietary constituents remained the same) from 2400-1200 (see protocol DOPA ▭). Animals 5, 6, and 7 received an inverse of this protocol; L-DOPA being present in the diet from 1200-2400 each day (see protocol ▭ DOPA). In both cases the animals received the control diet for the 12 h interval of each day when DOPA was not administered. The bottom animal received the L-DOPA diet ad libitum (DOPA FF).

Figure 2. Data from Figure 1 is statistically fitted to a cosine function (cosinor) and is shown graphically. The outer band on the clock's face gives the clock hour, while the inner band (subdivided into hours) gives the feeding protocol (FS-cycle). The hands of the clock point to the time of day (outer band) at which the circadian oscillation reaches its peak (acrophase); the length of the hands gives the amplitude (°C, see scale center of right hemisphere) of the oscillation; the radius within the ellipse (distal end of clock's hand) gives the 99% confidence interval for error in the amplitude; the variation in clock hours defined by the hashed lines tangent to each ellipse/gives the error in time of acrophase: for Figure 1 (A) entrainment only, days 6-11; (B) DOPA FF (ad libitum DOPA), days 13-17; (C) control diet (24% protein), days 13-17; (D) DOPA 2400-1200, No DOPA 1200-2400, days 13-17; (E) DOPA 1200-2400, No DOPA 2400-1200, days 13-17.

represents the 99% confidence arc and

Figure 3. A cosinor evaluation of animals in Figure 1; [fifth from top (A), sixth from top (B), seventh from top (C)] is shown for days 13-17.

Figure 4. The consequences of feeding L-DOPA during early active and late active phases of the circadian cycle are shown graphically. The administration of L-DOPA after the thermal acrophase (bottom middle) results in the maintainence of a good circadian rhythm (euchronic) as is conventionally seen in control animals (bottom left). However, when L-DOPA is given before the thermal acrophase a dyschronic (nearly phaseless) condition results (bottom right). The figure's upper portion graphically displays the catecholamine pathway (to the peak of the active phase) from tyrosine (TYR) to epinephrine (EPI) and the indoleamine pathway (inactive phase) from tryptophan (TRY) to serotonin (SER). When DOPA enters the metabolic pathway during the early active phase, the catecholamine pathway is shut down (chronotypic pathway block) resulting in circadian dyschronism.

Figure 5. Telemetry tracings of intraperitoneal temperatures for 7 rats measured every 20 min is shown for 12 days. Following entrainment for several days (DL 16:8, FS 8:16; not shown), the animals are subjected to alternate days of "feasting" and "fasting" (days 11, 12, 13, and 14) prior to receiving a regimen of L-DOPA in the diet (see top of graph for LD and FS protocols). Room light was continuously dim after 0900 on day 13. On day 15, the feeding regimen resumes. The F-phase of the regimen is subdivided into an early feeding (F_1) of 3 h duration from 0900-1200 and a later feeding (F_2) of only 1 h from 1600-1700, separated by 4 h of starvation. The top animal remained as a control throughout the entire experiment, receiving only the 24% protein control diet. The animals below, grouped in 3's, received a diet containing 30 mg L-DOPA/g chow either in

the late feeding phase (DOPA in F_2, top group of 3) or in the early phase (DOPA in F_1, bottom group of 3). Animals received the control diet in the phases when DOPA was absent. Arrows indicate the time at which DOPA was administered each day.

Figure 6. A cosinor evaluation of Figure 5, days 19, 20, and 21, is shown for (A) DOPA in F_2, and (B) DOPA in F_1 groups.

Figure 7. Telemetry tracings of intraperitoneal temperatures measured every 20 min for 12 days is shown for 7 rats. Following entrainment for several days (LD 8:16, FS 8:16; not shown) the animals are subjected to alternate days of "feasting" and "fasting" (days 11, 12, 13, and 14) prior to receiving a regimen of L-DOPA in the diet (see top of graph for LD and FS protocols). Room light remained continuously dim after 0900 on day 13. On day 15 resumption of the feeding regimen (FS 8:16 as during entrainment) is accompanied by a phase shift ($\Delta\Phi$-6 h) in the FS-cycle. The top animal (control) received only the 24% protein control diet throughout the balance of the experiment. The animals below subdivided into groups of 3 were given L-DOPA in the diet at a concentration of 30 mg L-DOPA/g chow. The upper group received L-DOPA only in the late (DOPA in F_2) feeding phase and control diet in F_1, while the lower group received L-DOPA only in the early (DOPA in F_1) phase. Arrows indicate the time at which L-DOPA was administered.

Figure 8. A cosinor summary of Figure 7, days 19, 20, and 21, is shown for (A) DOPA in F_2, and (B) DOPA in F_1 groups.

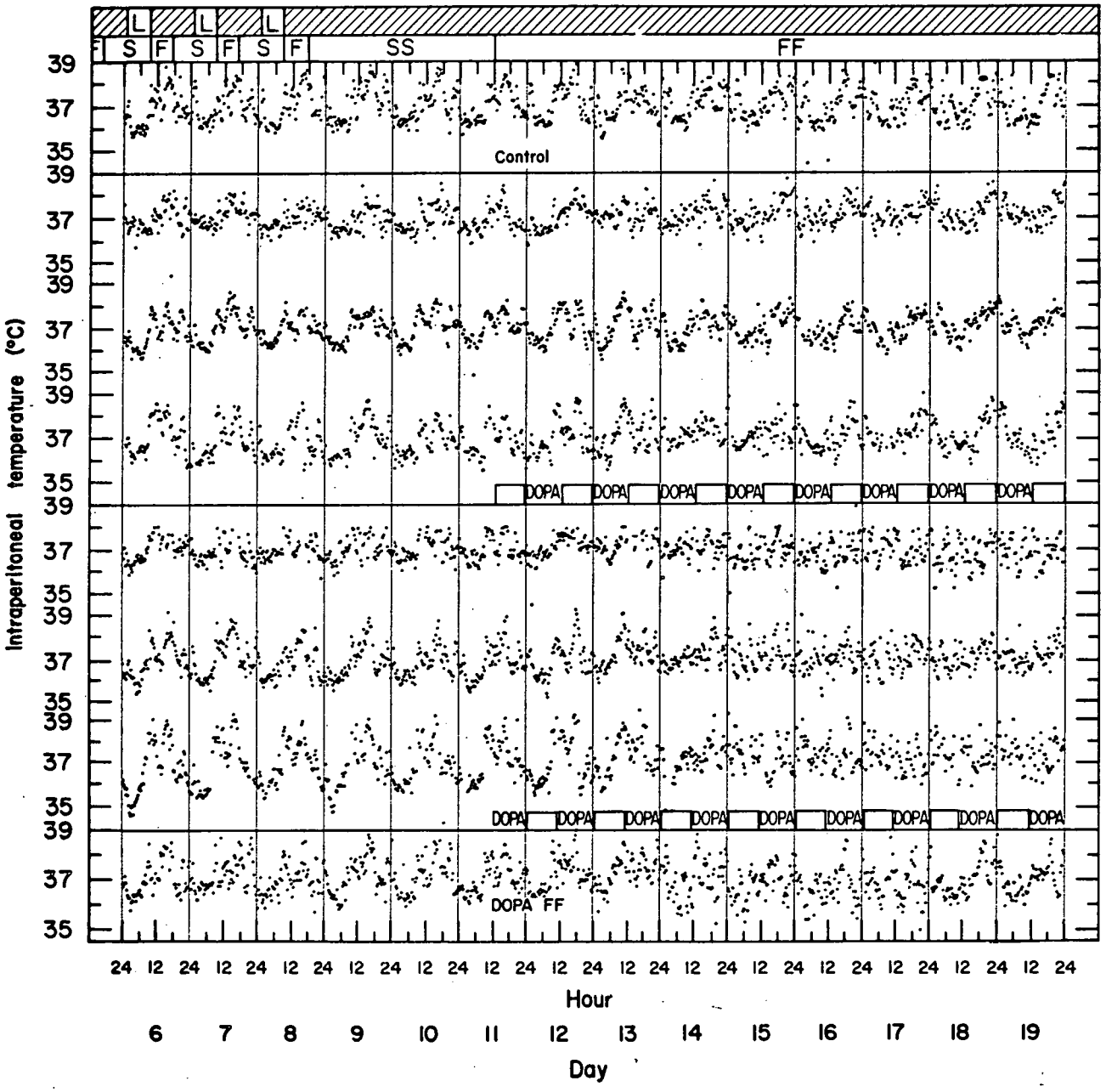
Figure 9. Telemetry tracings of intraperitoneal temperatures measured every 20 min is shown for 6 animals over 12 days. Following entrainment for several days (LD 8:16, FS 8:16; not shown), the animals are subjected to alternate days of "feasting" and "fasting" (days 11, 12, 13, and 14) prior to receiving

a regimen of L-DOPA in the diet (see top and middle bars for LD and FS protocols). On day 15 the animals in the upper portion of the graph resume program feeding (FS 8:16) after a phase shift of 12 h ($\Delta\Phi$-12 h) in the feeding protocol; and on day 16 the animal, in the lower portion after an 18 h shift ($\Delta\Phi$-18 h = +6 h). The top animal (control) in each portion received only the 24% protein control diet during the experiment. The middle and lower animals in each section received a diet containing 30 mg L-DOPA/g chow at either the late (DOPA in F_2) feeding phase (middle animals) or in the early (DOPA in F_1) phase of the FS-cycle (lower animals); control diet was fed in alternate phases when DOPA was absent. Arrows indicate the time of administration of the L-DOPA diet.

Figure 10. A cosinor summary of Figure 9 (top), days 20, 21, and 22, is shown for (A) DOPA in F_2, and (B) DOPA in F_1 animals.

Figure 11. A cosinor summary of Figure 9 (bottom), days 20, 21, 22, is shown for (A) DOPA in F_1, and (B) DOPA in F_2 animals.

Fig 1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Control
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Intraperitoneal temperature (°C)
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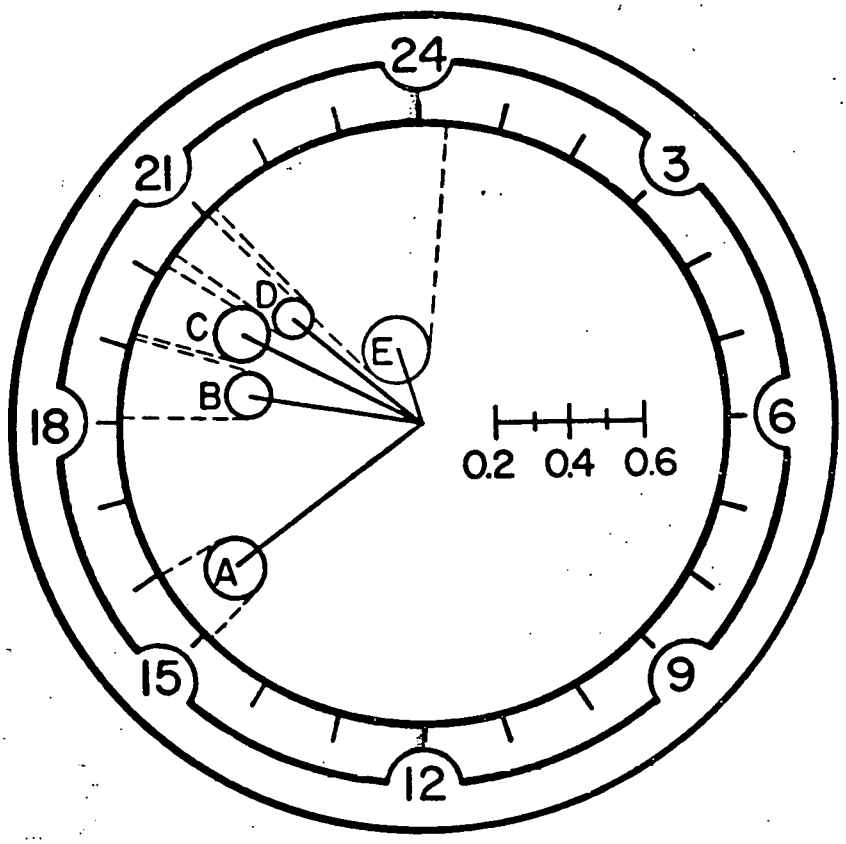
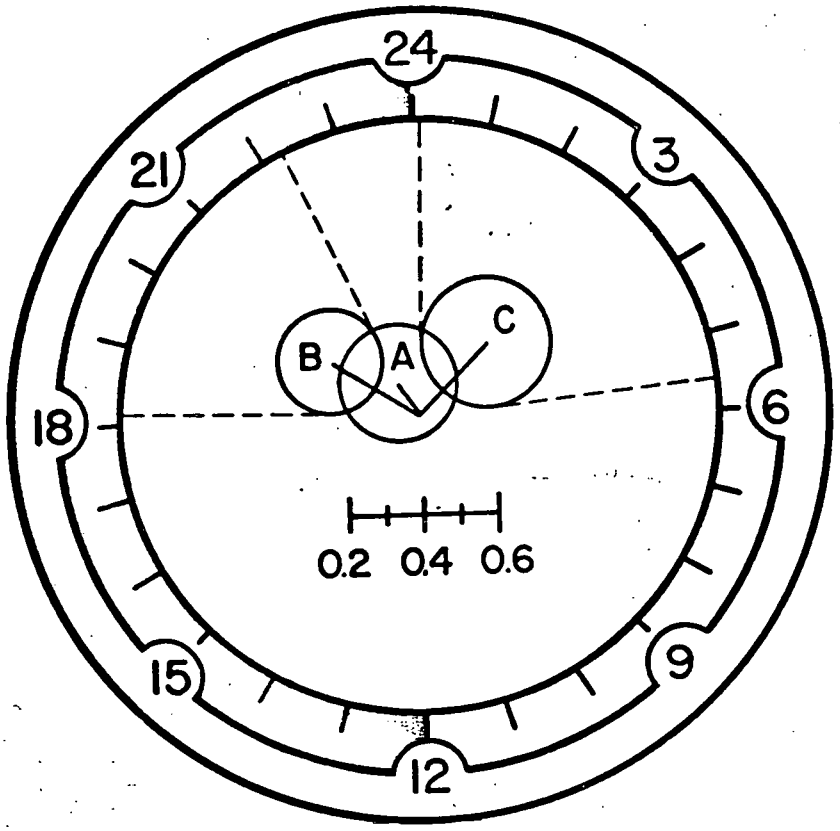
Day

Fig 2



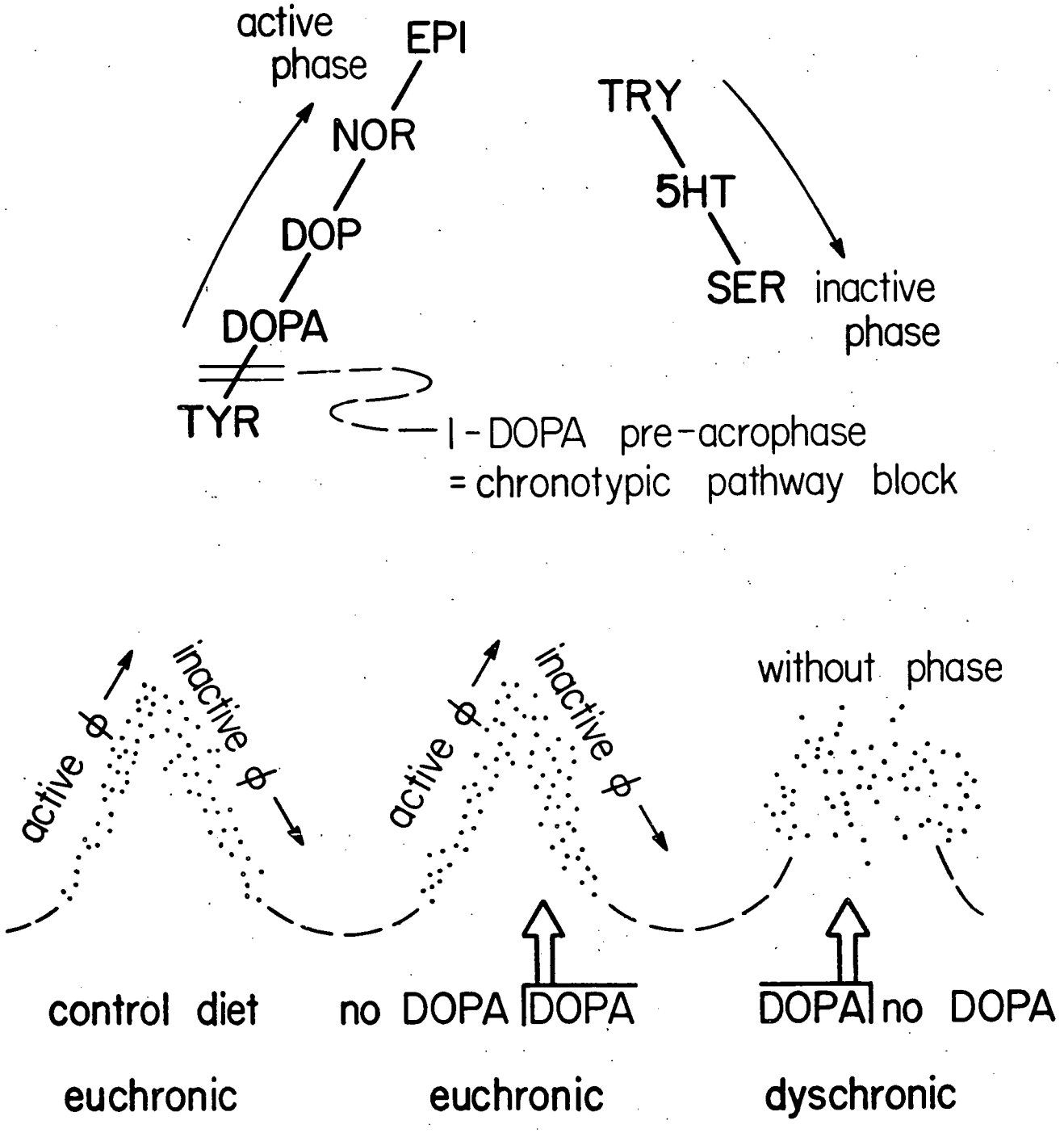
	N	ϕ (h)	99%CA (±m)	A (°C)	99%CI (±°C)	P
A	7	1529	31	.60	.16	.0001
B	9	1837	31	.44	.12	.0001
C	7	1848	33	.51	.14	.0001
D	8	2038	34	.42	.11	.0001
E	7	2241	100	.19	.18	.0001

Fig 3



	N	ϕ (h)	99%CA (±m)	A (°C)	99%CI (±°C)	P
A	1	2139	DYS	.10	.30	.1110
B	1	2010	123	.26	.28	.0001
C	1	0251	163	.25	.34	.0001

Fig 4


active phase
EPI
NOR
DOP
DOPA
TYR
TRY
5HT
SER
inactive phase
l-DOPA pre-acrophase
= chronotypic pathway block
active ϕ
inactive ϕ
active ϕ
inactive ϕ
without phase
control diet
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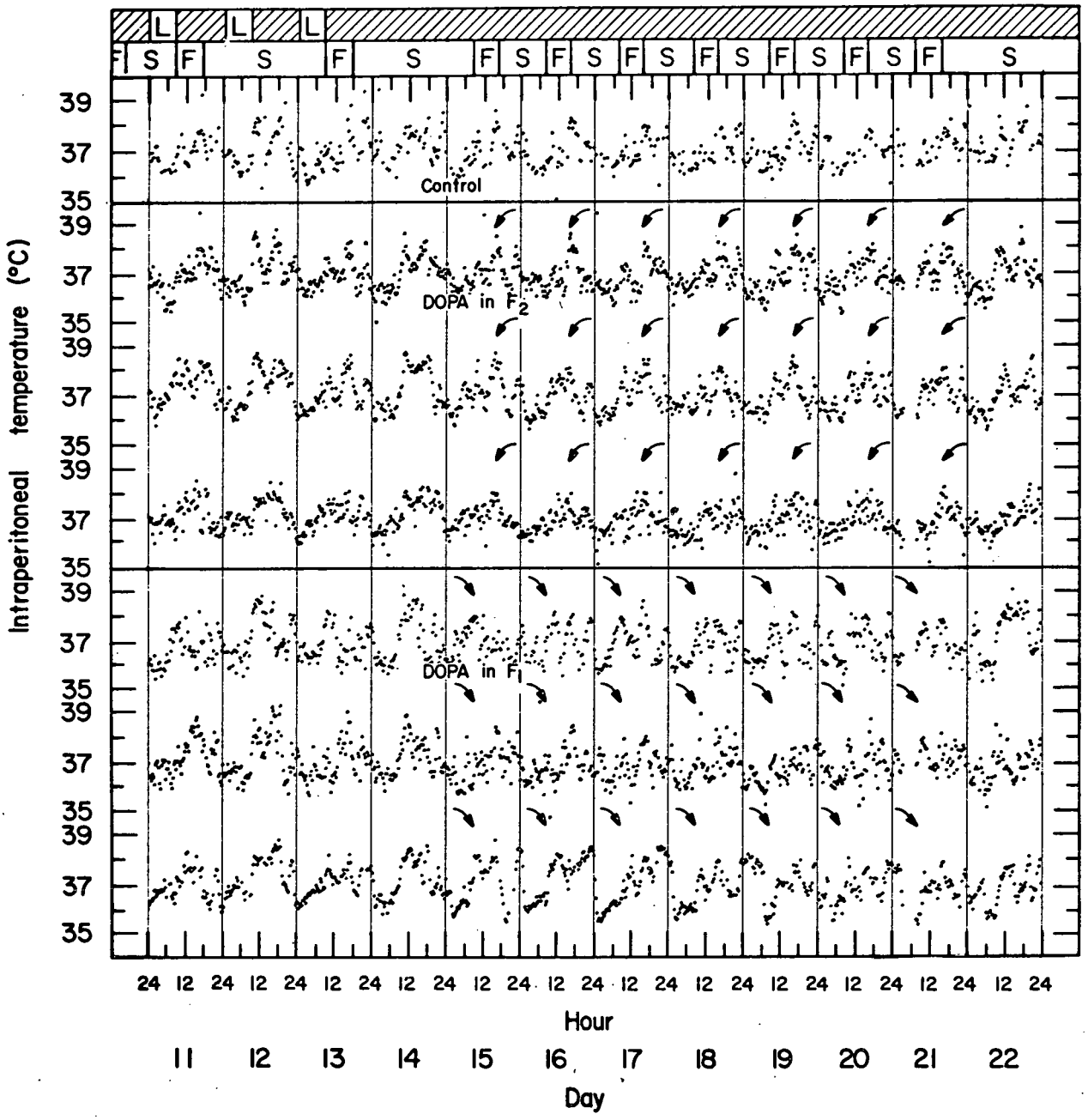
DOPA
DOPA
no DOPA
euchronic
euchronic
dyschronic

Fig 5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Control
DOPA in F2
DOPA in F1
Intraperitoneal temperature (°C)
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Hour
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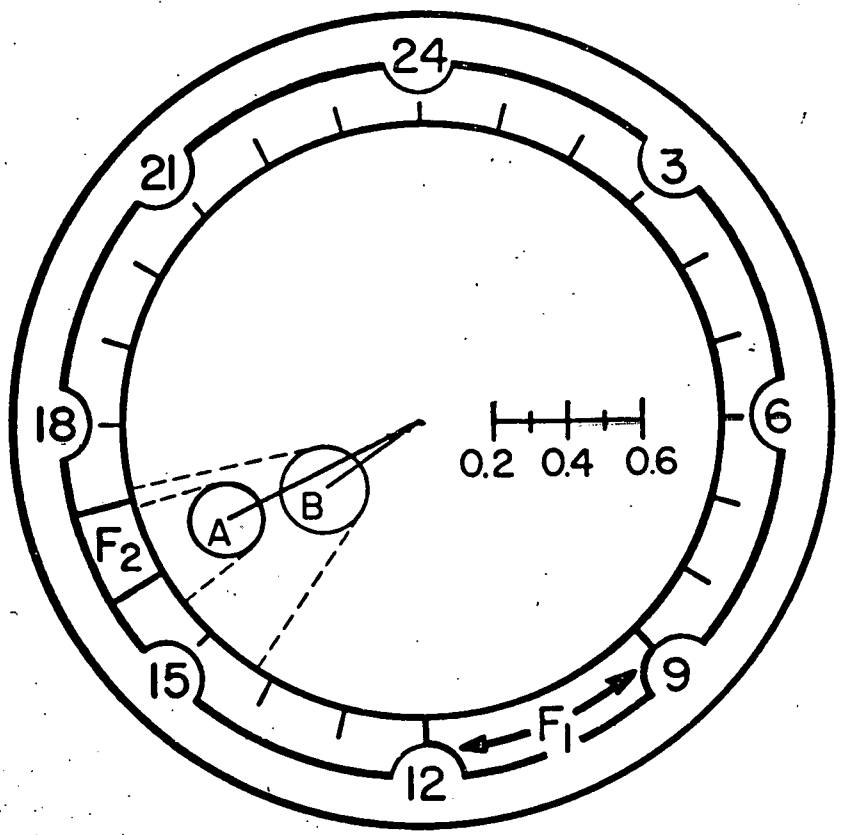
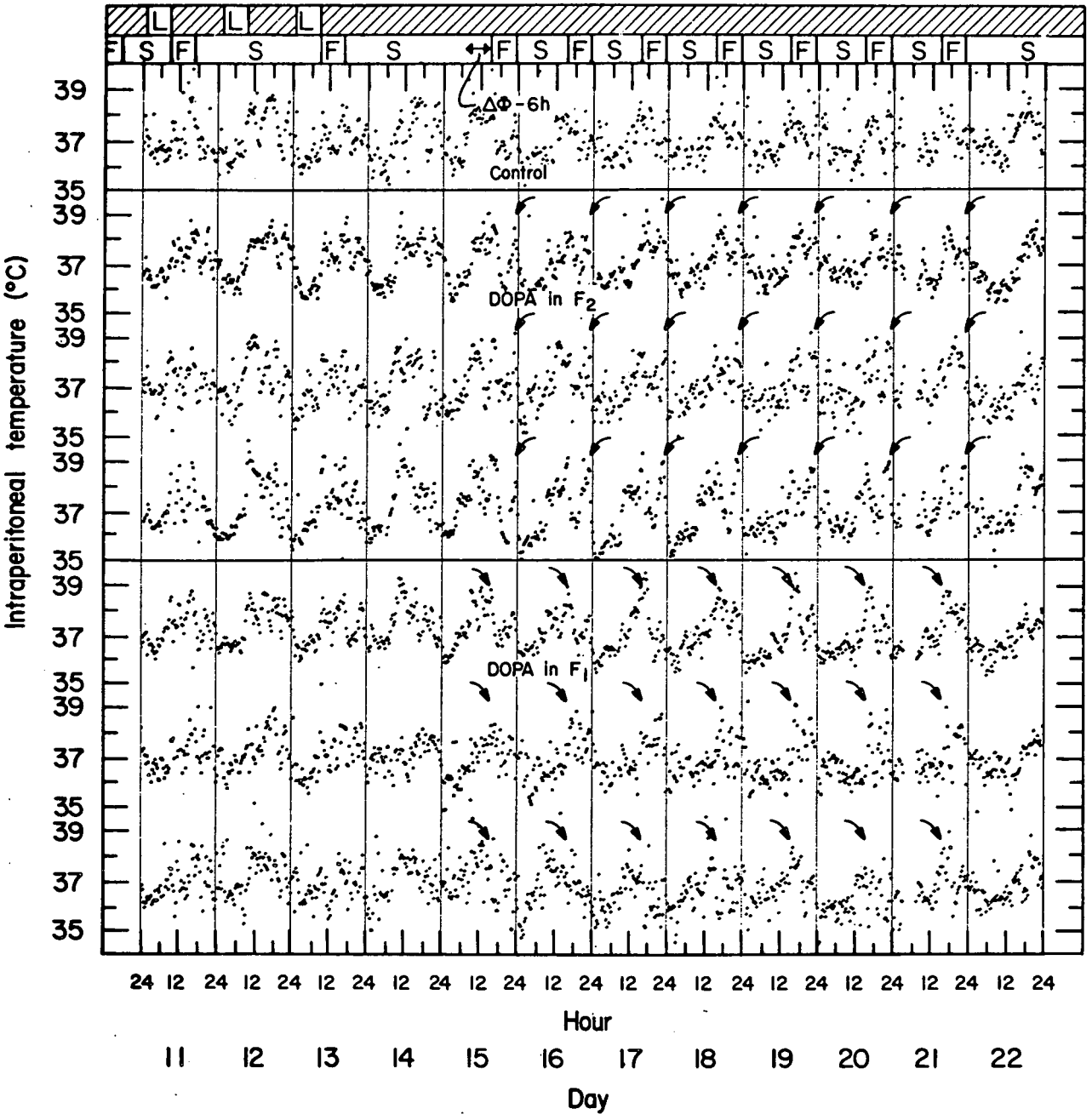
Day

Fig 6



	N	ϕ (h)	99%CA (±m)	A (°C)	99%CI (±°C)	P
A	4	1616	41	.55	.20	.0001
B	4	1543	87	.30	.22	.0001

Fig 7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ΔΦ -6h
Control
DOPA in F2
DOPA in F1
Intraperitoneal temperature (°C)
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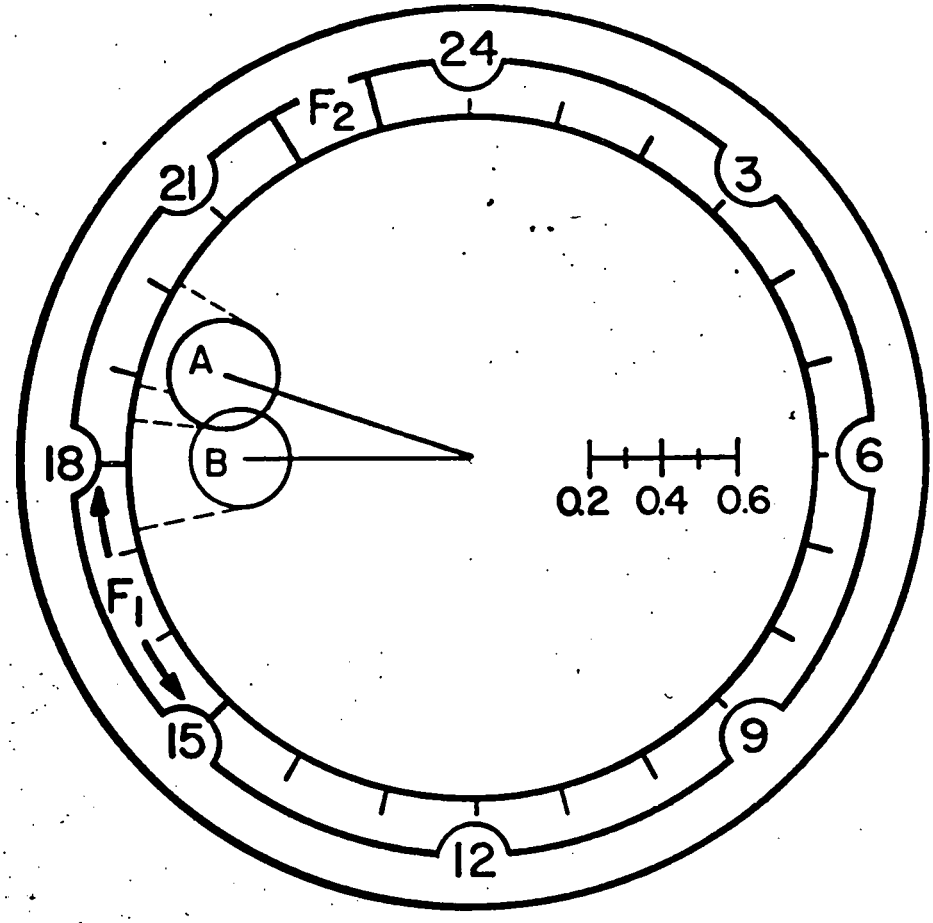
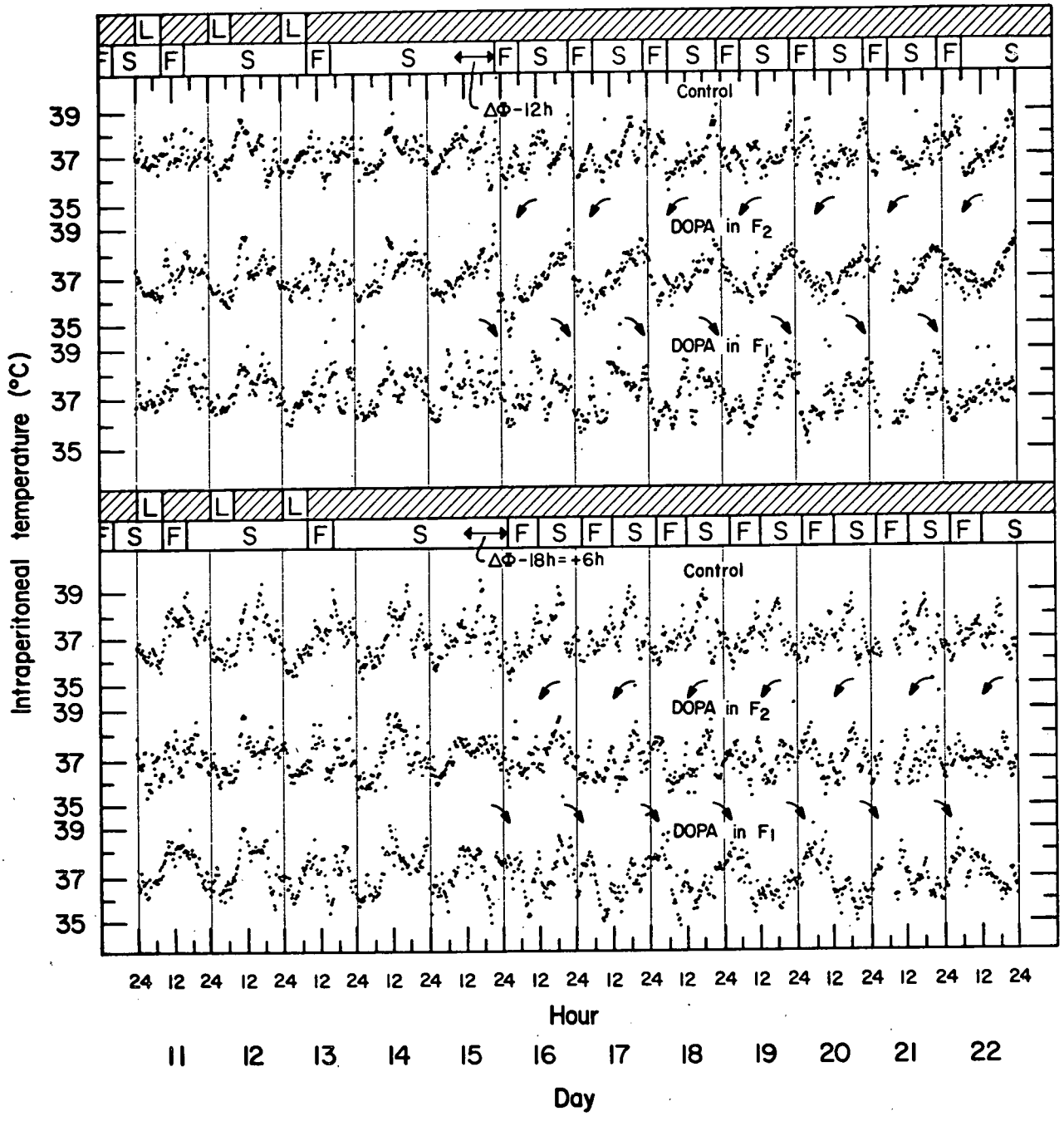
24 12 24 12 24 12 24 12 24 12 24 12 24 12 24 12 24 12 24 12 24 12 24 12 24
Hour
11 12 13 14 15 16 17 18 19 20 21 22
Day

Fig 8



	N	ϕ (h)	99%CA (±m)	A (°C)	99%CI (±°C)	P
A	4	1917	49	.67	.36	.0001
B	4	1804	50	.58	.31	.0001

Fig 9


L
S
F
ΔΦ-12h
Control
DOPA in F2
DOPA in F1
ΔΦ-18h=+6h
Intraperitoneal temperature (°C)
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37
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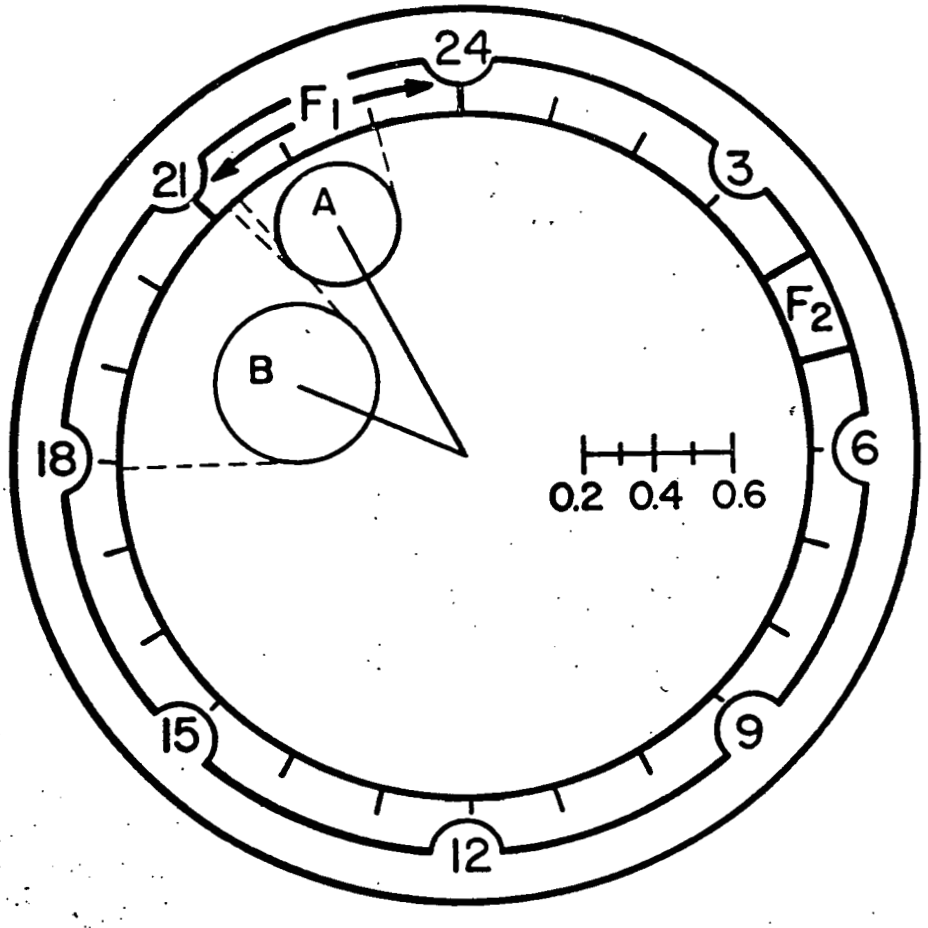
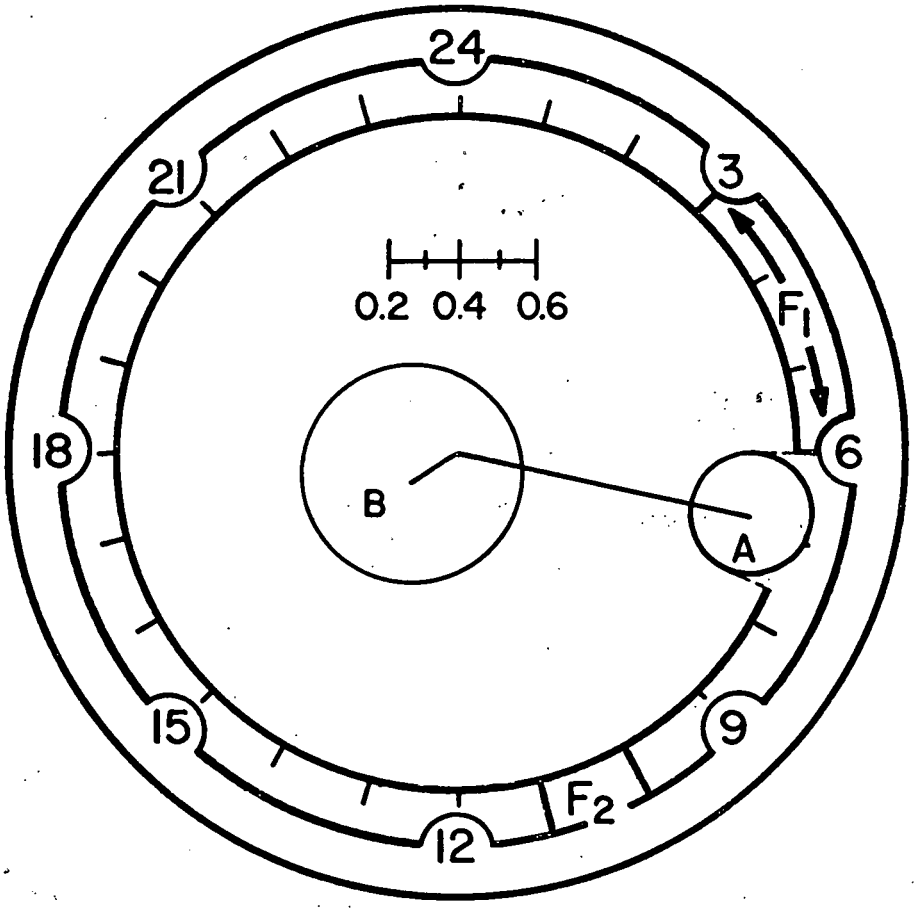
24 12 24 12 24 12 24 12 24 12 24 12 24 12 24 12 24 12 24 12 24 12 24
Hour
11 12 13 14 15 16 17 18 19 20 21 22
Day

Fig 10



	N	φ (h)	99%CA (±m)	A (°C)	99%CI (±°C)	P
A	2	2207	57	.58	.31	.0001
B	2	1934	101	.67	.40	.0001

Fig 11



	N	ϕ (h)	99%CA (±m)	A (°C)	99%CI (±°C)	P
A	2	0644	47	.76	.32	.0001
B	2	1603	DYS	.14	.56	.3080