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TOWARD CHRONO-PHARMACOLOGY

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Proceedings of a satellite symposium to the 8th International Congress of Pharmacology, Nagasaki, Japan, 27-28 July 1981

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Volume 41

TOWARD CHRONOPHARMACOLOGY

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PREFACE

TOWARD CHRONOPHARMACOLOGY, a Satellite Symposium to the 8th International Congress of Pharmacology, held in Nagasaki, Japan, advanced further the recognition and appreciation of the need for timing in the study of drug activity and in therapy. The two-day conference addressed new and innovative approaches toward neuro-pharmacology. It included reports on circadian rhythms in brain neurotransmitters and their possible involvement in coordination of behavioral activity. Scientists from Tallahassee, Florida, introduced data on circadian variations in β-endorphins, thus establishing a foundation for explaining circadian changes in physiologic variables coordinated by endogenous opiates--variables such as pain, euphoria and analgesia. The Floridian laboratory also explored a possible role of circadian rhythms in dopamine with respect to convulsions produced experimentally by anticonvulsive drugs. Scholars from Nagasaki, Japan, discussed the possibility of chronotherapy in clinical psychiatry. The group from the Argonne Laboratories in Lamont, Illinois, presented convincing information on the chronobiotic action of catecholamines and their possible future role in coordinating timing within the organism--euchronism and dyschronism.

Additional important studies discussed involved the cardiovascular and circulatory system and included the chronopathology of salt and blood pressure elevation and the influence of loads on circadian rhythms of ventricular weight vs. body weight, as influenced by angiotensin. The chronopharmacokinetics of β-arrhythmias were also introduced.

Scientists from Minneapolis, Minnesota; Tallahassee, Florida; and Little Rock, Arkansas, documented the chronobiology and clinical implication of ACTH 1-17 and the role of insulin and glucagon in DNA labelling. Investigators from Nottingham, England, introduced a method for the computer analysis of chronotherapeutic data. This same group confirmed the occurrence of rhythms in renal allograft rejection and emphasized the need for timing immunosuppressive therapy.

The chronopharmacology embraced at this conference constitutes a further step towards a more basic and necessary approach to health care and the emerging science of chronotherapeutics.

CONTENTS

I. Neurochronopharmacology

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Effects of Psychotropics on Circadian Motor Activity in Rats

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ABSTRACT

Chronopharmacology, which, in one sense, deals with temporal change of biological functions as affected by drugs, potentially provides ways of seeking for new types of drug and elucidating mechanisms of drug action. By using a system monitoring motor activity and drinking behavior, we investigated the effect of psychotropics on circadian activity of Fischer rats. Four kinds of drug dissolved in drinking water were tested for more than one month. 0.05% FS-32 and 0.01% morphine seldom affected the activity. 0.10% Cocaine increased the activity. Only 0.01% *d*-amphetamine (Amp) revealed marked effects as follows. Amp first caused rats to get into what we call Amp-Stage-I characterized by the morning peak progressively augmentated and delayed with the passage of days. In the ensuing days (Amp-Stage-II), the activity level varied largely every other day — circabidian rhythm. Phase-jump-like phenomenon occurred in the advanced experiment lasting longer, suggesting the interaction between two circadian components. All these tendencies observed in LD 12:12 were reproduced also in DD. The rats freed from Amp in Stage-II, regained the normal circadian activity in a few days. Restart of Amp treatment, however, caused the rats to get directly into Stage-II, skipping over Stage-I — reversal tolerance or innervation supersensitivity.

KEYWORDS

Circadian; circabidian; phase jump; reversal tolerance; innervation supersensitivity; motor activity; *d*-amphetamine; cocaine; FS-32; morphine.

INTRODUCTION

Circadian rhythm is innate and so stable as to resist exogenous stimuli such as electroshock or chemicals (Richter, 1965). This rhythm, nevertheless, seems to leave room to be modulated to some extent by some kinds of psychotropic drug. A tranquillizer, (3-alkyl pyrazolyl)piperazine (Simpson *et al*, 1973), and the anti-depressant, imipramine (Buchsbaum, 1979) are said to be effective for recovery from physiological disorders and decline of performance in man caused by time-zone shift. Wehr *et al* (1979) reported that imipramine shortened the circadian period in rats. A long-term administration of phenobarbital resulted in the so-called dyschronism in rats under DD (Ehret *et al*, 1977). Lithium ion affected circadian rhythm in the

blinded rat to lengthen its period (Kripke and Wyborney,1980). A possibility was suggested by Wahlström and Widerlöv (1968) and Bodman (1970) that *d*-amphetamine lengthens the freeruning circadian period in canary and in mice and rats, respectively.

A view that encourages us to investigate the effect of psychotropics was proposed by Halberg (1968) and Scheving (1980) suggesting that some illnesses, including emotional ones, may be strongly associated with disorder of temporal relationship between physisological functions.

Pertaining to the effect of *d*-amphetamine found to be most influential over the activity rhythm of rats among other psychotropics tested, this report includes new experimental results suggesting that there may be at least two kinds of oscillation underlying the circadian activity; one is more apt to undergo the influence of this drug than the other. Chronobiological evidences concerning reversal tolerance or innervation supersensitivity also will be reported.

METHODS

Animal. Male Fischer rats (18-20 weeks old at the beginning of experiment) were used. Throughout the experimental days, the animals were housed individually in plastic cages (22 x 38 x 24 cm) substrated with wood shavings. Solid food and drinking water were so prepared that rats may eat and drink *ad libitum*. Temperature was 24-25°C and relative humidity 50-60%. Rats received LD 12:12 unless otherwise stated. Light intensity in the light fraction of LD cycle was about 1,000 lux produced by a 10-watt fluorescent white lamp.

Apparatus. The central part of the activity monitoring system is a tilting-cage-actograph, which is sensitive to the horizontal movement of an animal, but neither to the vertical one nor to behavior such as grooming, so that the noise may be minimized. The actograph is equipped with a drinkometer (Kuribara *et al*, 1978). Outputs from the actograph and the drinkometer are in a circuit with digital printer as well as an event recorder. The printer printed out the numerical data every 15 min for the activity and every day or every 15 min for the water consumption. Each actograph with a drinkometer was set in a sound-attenuating box, so the rats could not see each other.

Drug administration. *d*-Amphetamine sulfate (Chugai), cocaine hydrochloride (Takeda), FS-32 developed by Ikeda *et al* (1979) and morphine hydrochloride (Sankyo) were tested. The drug was dissolved in drinking water. The vehicle of drug was 0.45% saline in Series I and distilled water in the other series. Drinking water with drug or saline was renewed every day. Experiment comprises three series. Methods specifically related to the series such as administration of drugs will be mentioned together with results.

RESULTS

Series I Screening of psychotropics. This series lasted for 110 days. Five rats for each lot were treated with 0.10% cocaine, 0.01% *d*-amphetamine (Amp), 0.05% FS-32, 0.01% morphine or their vehicle (0.45% saline) from day 37 to 80. Thereafter all rats were freed from the drugs and vehicle.

Rats in all lots showed diphasic activity pattern with morning meak as major and evening peak (Fig. 1). Cocaine increased the activity to more than 150%, but did not change the phase of two peaks. Amp augmentated the morning peak which apparently freeran into the light fraction. Morphine and FS-32 had no significant effect, but one of five morphine-treated rats often showed activity which seems to

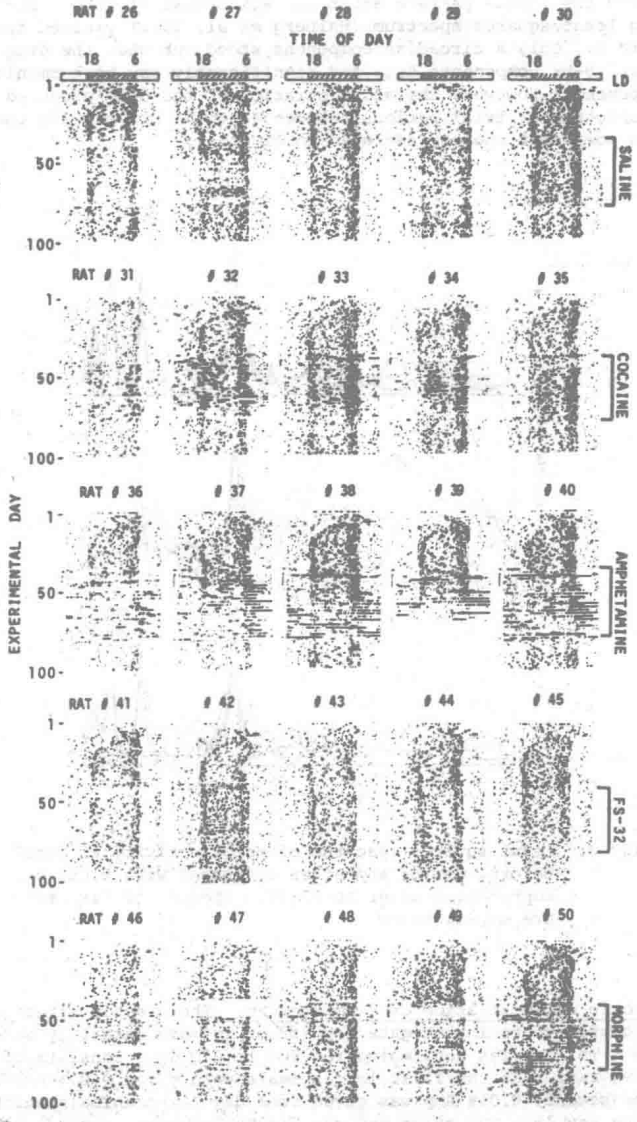

Fig. 1. The actograms of rats consuming psychotropics in LD. 0.10% Cocaine, 0.01% *d*-amphetamine, 0.05% FS-32, 0.01% morphine or their vehicle (0.45% saline) dissolved in drinking water was given from day 37 to 80. Five rats received the treatment with a given drug.

be desynchronized with LD cycle (Rat #50). The activity which underwent the drug effect recovered the normal pattern after the withdrawal of drug. Statistical analysis using least squares spectrum (Halberg *et al*, 1972) yielded the result shown in Figure 2. Only a circadian component stood out when the drug was not given; 12-hr and 8-hr components detected significantly may be harmonics of the circadian component. However, the administration of the drug produced prominent peaks in the spectrum at trial periods between 48 to 55 hr, showing the existence of circabidian component one may see also in Figure 1.

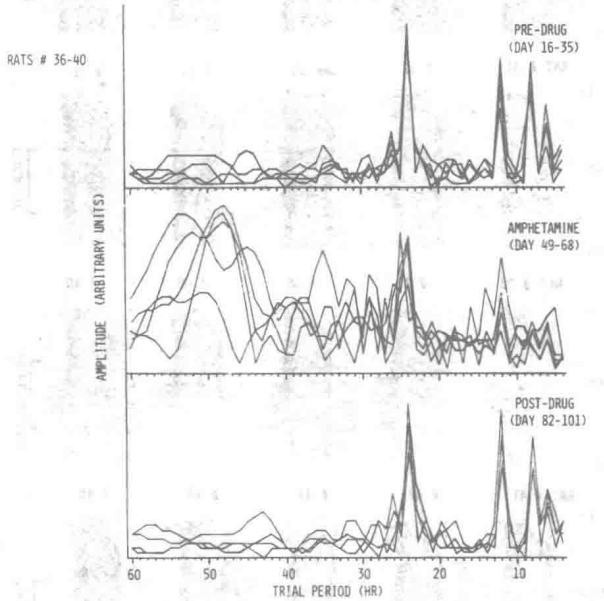

Fig. 2. Least squares spectrum of motor activity in rats before, during and after treatment with 0.01% *d*-amphetamine under LD 12:12. Spectra of five rats are superimposed.

Series II Chronic administration of *d*-amphtamine. The drastic effect of Amp found in Series I prompted us to investigate the effect in more detail by chronic administration. This series continuing for 200 to 370 days consists of four lots, each having five rats. In the first lot, animals were given 0.01% Amp from day 32 to 270. In the second, 0.01% Amp was given from day 32 to animals which had been held in DD since day 18. The third and the fourth lots were control held in LD and in DD, respectively, throughout the experimental days without administration of drug.

Points clarified commonly in both LD and DD are as follows(Fig.3). Amp first brought about what we call Amp-Stage-I, in which the morning peak was progressively augmentated and delayed with the passage of days. In the ensuing days (Amp-Stage-II), high and long-lasting activity occurred almost every other day — the circabidian phenomenon. This stage would be characterized visually also by two

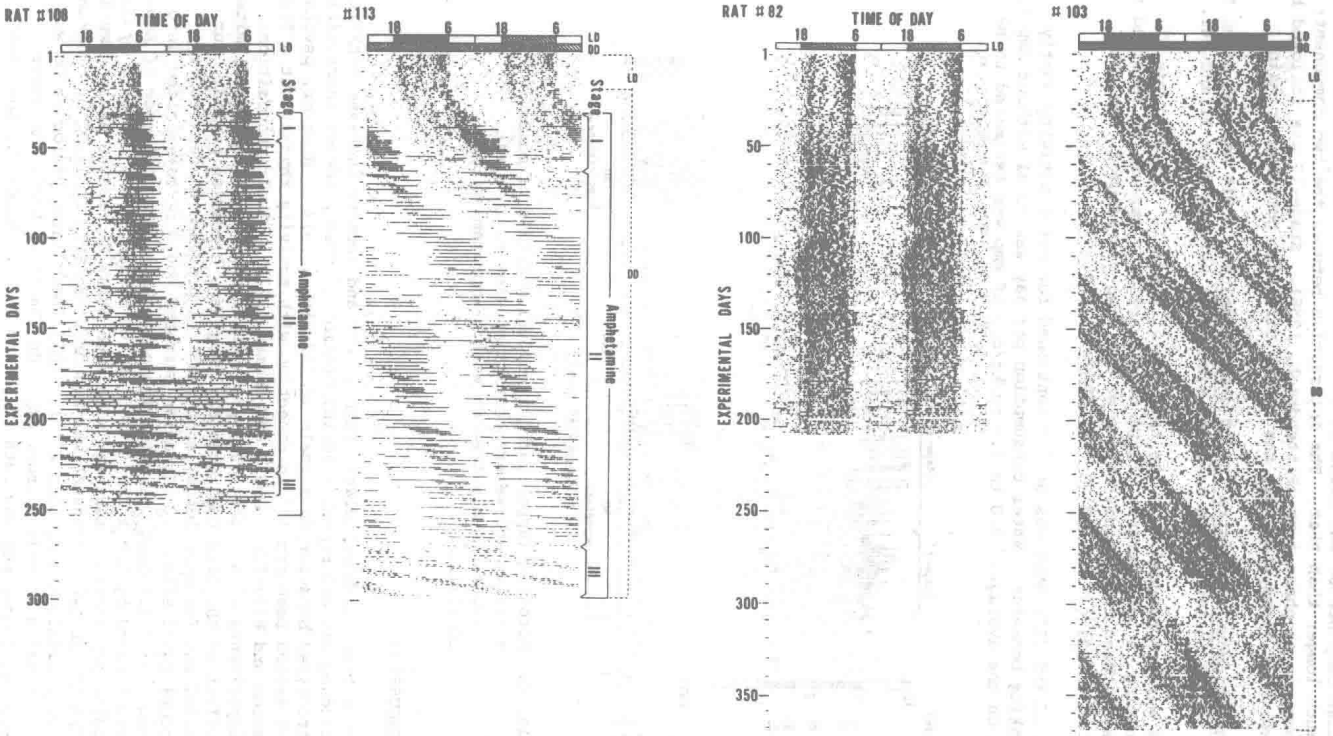

Fig. 3. Left panels: the actograms of rats treated chronically with 0.01% *d*-amphetamine in LD 12:12 (#108) and in DD (#113). Right panels (controls): the actograms of rats receiving no drug in LS 12:12 (#82) and in DD (#103).

kinds of circadian components; one looks to be 24 hr in LD or close to 24 hr in DD and the other much longer than that. The interaction between the two components produced a phenomenon as phase jump (Pittendrigh, 1958). Stage-II was followed by Stage-III, in which it seems that only the longer circadian component remains.

Series III Discontinuous administration of *d*-amphetamine. 0.01% Amp was given to five rats from day 18 to 170 with a temporal withdrawal between days 91 and 141.

Stages I and II were reproduced. In the half way of Stage-II, the drug was withdrawn, resulting in reappearance of the normal activity pattern as recorded for the first 17 days. When the administration of the drug was resumed, the rat immidiately got into Stage-II, skipping over Stage-I (Fig. 4).

In both Series II and III, what was so far mentioned for motor activity mostly applies to drinking behavior. Water consumption per day was 23 ml without Amp and 10 ml with Amp on the average. 3.0 to 3.5 mg/kg/day of Amp was estimated to be ingested.

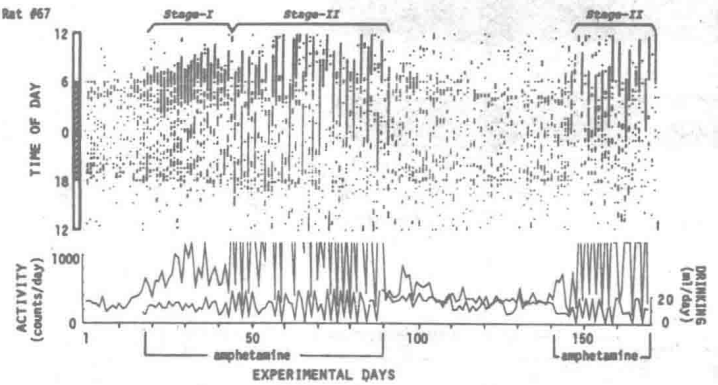

Fig. 4. Actogram (upper panel), and daily totals of motor activity and water consumption (lower) in a rat discontinuously treated with *d*-amphetamine under LD 12:12.

DISCUSSION

It has been known that psychostimulants such as Amp and cocaine increase activity of animals including man and repeated administration of them produces intoxication in man and stereotyped behavior in animals (Schiørriong, 1977). However, psychostimulants have seldom been studied in conection with activity rhythm, but a few works by Wahlström and Widerlöv (1968), and Bodman (1970). Their propositions based on the experiments of a couple of days or about two weeks long were limited simply to an effect of the drug that possibly lengthens circadian period. Our experiment carried out for much longer span than the predessors' resulted in finding more complicated effects. Circadian patterns could be categorized into Stages I, II and III progressing one after the other under the influence of Amp. Stage-I is characterized by the augmentation of the morning peak, Stage-II by the two kinds of circadian components interacted with each other to produce phase-jump-like phenomenon. One of the two components was synchronized with LD 12:12 or freeran in DD at the period a little longer than 24 hr. This freerunning period in DD with Amp took a similar value to that without Amp. On the other hand, the other component freeran at longer periods both in LD and in DD, indicating that this

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