PSYCHOPHARMACOLOGY HANDBOOK · VOLUME III

Animal Research in Psychopharmacology

A Compilation from the Available World Literature for 1961

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE • Public Health Service

PSYCHOPHARMACOLOGY HANDBOOK • VOLUME III • 1961

Animal Research in Psychopharmacology

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PREFACE

This handbook is a compilation from the literature on animal psychopharmacology published in 1961 and available to the Western World.[1] Research articles analyzed for inclusion in the handbook were limited to those published in recognized journals and government reports. Titles were obtained by searching *Chemical Abstracts, Index Medicus, Excerpta Medica, Current Contents,* and the accession list of the Psychopharmacology Service Center of the National Institute of Mental Health. Accessory sources included bibliographies of major review articles and other publications.

The papers selected report the effects of psychoactive drugs (broadly defined) on animal behavior. Papers on physiology were included if they involved primarily central nervous system effects. Studies on isolated organs or tissues, *per se* (as opposed to the intact animal), have been excluded. Only those CNS drugs that primarily affect voluntary and emotional behavior have been included. Thus, anticonvulsants, general anesthetics, classical muscle relaxants, and autonomic agents have not been considered unless they also influence mood or behavior to a considerable degree.

Related research results from the world literature (for example, the effects of chlorpromazine on the behavior of the cat) are grouped under a few key categories. The categories used are (1) the drug, (2) the animal group, and (3) the type of measure or method employed in the study (i.e., behavioral, neurological, or physiological). Common laboratory mammals are grouped by species (cat, dog, guinea pig, hamster, mouse, rabbit, rat); other animals are grouped in larger classes (amphibian, bird, fish, invertebrate, primate). Grouping by experimental animal in the present volume differs from the arrangement used in previous volumes by the omission of secondary subdivisions under Amphibian, Bird, and Rodent.

Under the appropriate key categories, each paper was broken down into one or more "entries." Each entry consists of a short summary of the relevant experimental procedure and the behavioral, neurological, or physiological effects of one drug in one animal group. The entries are arranged alphabetically by (1) chemical name, (2) method employed in the study, (3) animal classification, and (4) senior author.

Each entry is prefaced by an entry number, a condensed bibliographic reference, and the dose range and route of administration. A complete bibliographic reference is given in the bibliography at the end of the volume; each bibliographic reference includes the entry numbers of all entries from each paper.

In general, separate entries were written each time a different drug, species, or class of criterion measure was reported in the same study. Thus, the number of entries for any single paper varies with the number of drugs, animal species, and classes of criterion measures reported.

Our approach in writing the entries was to state the procedure and results of each experiment as objectively as possible; no interpretation was attempted beyond noting conditions that seemed most relevant for understanding the procedure and results of the study.

Several facts are uniformly reported if they were unambiguously given in the study; these include the number of subjects in the study, the nature and values of conditioned and unconditioned stimuli, criterion measures of performance, dose-response and dose-time variables, and side effects. Other facts are reported only when they appear relevant.

(1) This handbook is preceded by Volumes I and II. The first volume, covering a selected portion of the literature on animal research in psychopharmacology, was assembled to evaluate the method of data presentation used in the present volume. One hundred copies of Volume I were printed by the Psychopharmacology Service Center and sent to various research workers for evaluation. That volume is now being revised and enlarged, and will be made available when completed. It will cover the literature from 1954 through 1959. Volume II (PHS publication No. 1006) is available for sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C., 20402, at a price of three dollars.

Investigators differed greatly in reporting procedural details. In particular, reporting of the number of animals used was frequently inadequate; brief reference to the species was often the only notation. When the number of animals per drug or per dose was mentioned, we gave the investigator the benefit of the doubt and reported the Ns (number of animals used) under the assumption that the figures given referred to discrete groups used only once.

Each drug or chemical substance included in an experiment usually received separate treatment, no matter how similar its action or chemical structure to that of some other compound. Thus, each of the phenothiazines is treated separately, as are the Rauwolfia derivatives. There are exceptions to this rule, however. Optical isomerism was not generally used as a basis for separate classification. Also, when preliminary testing of a series of related compounds was reported, and only one or two of the compounds in the series were of interest, the results for the rest of the series were subsumed under the entries for the effective compounds or under a general class name. Entries were written for endogenous substances, such as epinephrine, GABA, etc., only if they were part of a study on psychoactive drugs, or if they were administered for the purpose of evaluating their effect on the behavior or physiology of the animal.

Nomenclature of compounds is that used by the World Health Organization (WHO), as published in the *International Dictionary of Drugs Used in Neurology and Psychiatry,* by C. M. Poser and V. Osbourn (Charles C. Thomas, Springfield, Illinois), when listed therein. For compounds not so listed, nomenclature is that of *The Merck Index* or the AMA-USP Nomenclature Committee (USAN). Compounds listed under different names by these three authorities are cross-indexed to the WHO name. Occasional compounds not listed in any of these sources have been identified in *Chemical Abstracts* or in *Pharmacological and Chemical Synonyms,* by E. E. J. Marler (Excerpta Medica Foundation, New York). Compounds for which no generic names are available are retained under their full chemical names, in the form used by *The Merck Index* or *Chemical Abstracts,* and the full chemical names of those alphabetized under generic names are included as subtitles under the generic name where this appears at the beginning of each section in the body of the Handbook. When compounds were administered as salts (e.g., amphetamine sulfate), the first mention of the compound within an entry gives the full name of the salt; subsequently, within that entry, the simple generic name alone is used to indicate that salt. If the drug is used in more than one form, this fact is specifically mentioned. Generic and trade names used by the authors of the papers reviewed are cross-indexed to the name used in the Handbook. A dictionary of drug names should be consulted for synonyms if a specific name is not found in the index.

In general, the abbreviations used conform to the standards of the *Style Manual for Biological Journals* (Conference of Biological Editors, AIBS, Washington, 1960).

Occasionally an author published the same data in more than one paper. In such cases, we did not report duplicate data.

In preparing this handbook, the assumption has been made that the behavioral effects of drugs are the results of an alteration by the drug of the entire organism-environment adjustment. This assumption has led to the inclusion of brief descriptions of stimulus parameters, training procedures, surgical preparations for experimentation, and methods of measurement or observation in the entries. Further experience may show that many such inclusions are irrelevant, but, without this knowledge, these variables were regarded as potentially effective ones.

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ABBREVIATIONS

ac	alternating current
Ach	acetylcholine
approx	approximately
ATP	adenosine triphosphate
avg	average
CAR	conditioned avoidance response(s)
CD50	convulsive dose in 50% of cases
CER	conditioned emotional response(s)
ChE	cholinesterase
cm	centimeter(s)
CNS	central nervous system
count/min	counts per minute
count/sec	counts per second
CPZ	chlorpromazine
CR	conditioned response(s)
crf	continuously reinforced
CS	conditioned stimulus
cycle/min	cycles per minute (electrical)
cycle/sec	cycles per second (electrical)
db	decibel(s)
dc	direct current
df	degrees of freedom
diam	diameter
DNA	desoxyribonucleic acid
DOPA	3,4-dihydroxyphenylalanine
drh	differential reinforcement of high rates
drl	differential reinforcement of low rates
ECG	electrocardiogram
ECS	electroconvulsive shock—seizure(s)
ED50	effective dose in 50% of cases
EEG	electroencephalogram
EMG	electromyogram
FI	fixed interval (of reinforcement)
FR	fixed ratio (of reinforcement)
ft	feet
g	gram(s)
GABA	γ-aminobutyric acid
GABOB	γ-amino-β-hydroxybutyric acid
HD50	hypnotic dose in 50% of cases
5-HIAA	5-hydroxyindoleacetic acid
hr	hour(s)
5-HT	5-hydroxytryptamine, serotonin
5-HTP	5-hydroxytryptophane
ID50	inhibitory dose in 50% of cases
im	intramuscular(ly)
ip	intraperitoneal(ly)
IRT	interresponse time
IU	international unit(s)
iv	intravenous(ly)
kg	kilogram(s)
LD50	lethal dose in 50% of cases
M	molar (solution)
ma, μa	milliampere(s), microampere(s)
MAO	monoamine oxidase
max	maximum, maximal
meq	milliequivalent(s)
mg, μg, ng	milligram(s), microgram(s), nanogram(s)
min	minute(s)
mix	mixed reinforcement schedule
ml, μl	milliliter(s), microliter(s)
MLD	minimum lethal dose
mm, mμ	millimeter(s), millimicron(s)
msec	millisecond(s)
mult	multiple reinforcement schedule
mv, μv	millivolt(s), microvolt(s)
μc	microcurie(s)
μf	microfarad(s)
N	number (of subjects)
NTP	normal temperature and pressure
P	probability
ParD50	paralyzing dose in 50% of cases
PD50	preventive dose in 50% of cases
pH	negative log concentration of hydrogen ions
po	oral(ly)
ppm	parts per million
rev/min	revolutions per minute
RNA	ribonucleic acid
RR	response-response interval
RQ	respiratory quotient
RS	response-shock interval
sc	subcutaneous(ly)
SD	standard deviation(s)
SD50	sedative dose in 50% of cases
SE	standard error(s)
sec	second(s)
SS	shock-shock interval
tand	tandem reinforcement schedule
temp	temperature
UCR	unconditioned response(s)
UCS	unconditioned stimulus
v	volt(s)
VI	variable interval reinforcement
vol	volume
VR	variable ratio reinforcement
w	watt(s)
wt	weight

CONTENTS

ACEPROMAZINE

2-Acetyl-10-(3-dimethylaminopropyl)phenothiazine

Behavior

DOG

1. RAPPEPORT, A. Y. Zh. Nevropatol. i Psikhiatr. *61*, 909–18 (1961)

Dose: 1–15 mg/kg im and iv.

Five min after 1 mg/kg acepromazine im, dogs (N=6, 10–23 kg) were ataxic; 30 min postdrug, they showed muscle weakness, but still reacted to sound; recovery was complete in 3½ hr. After 4–13 mg/kg im, they exhibited stupor, catatonia, increased muscle tonus, waxy flexibility, and did not respond to external stimuli for 1½ hr; subsequently they became hypotonic and comatose, with fine tremors. The same symptoms, with a more rapid course, were seen in 1 dog after 1 mg/kg iv. Aggressiveness and motor excitement, sometimes with vomiting, urination, and hypersalivation, were noted in some experiments in all subjects. After 6–15 mg/kg im, a previously established alimentary CR (CS=bell, 120/min metronome, flashing light, light, bubbling sound; USC=food) was lost for 24 hr by all subjects. After 1–3 mg/kg im, motor response was slowed and latency of CR increased for 3–4 days in all subjects. The effect of intermediate doses varied with the personality pattern of the subjects. In general, though all subjects lost CR_+ and most lost differentiation, paradoxical responses were seen only in the "weak" type; CR was fully reestablished in the "strong" type within 24 hr, in the "strong unstable" type within 48 hr, and in the "weak" type only after 4–8 days. After 1 mg/kg iv in 1 "weak" dog, CR to all stimuli was absent for 24 hr, CR to all CS_+ was slowed for 2 days, and CR to buzzer (1 CS_+) was lost or slowed for 4 days.

MOUSE

2. BIENFET, V., et al. Acta Neurol. Psychiat. Belg. *61*, 669–85 (1961)

Dose: 1–10 mg/kg ip and po.

The minimum dose of acepromazine which significantly influenced spontaneous activity and reactivity to stimuli was 1 mg/kg ip in mice (N not given). In other tests, spontaneous activity was reduced to 10% of control levels during the first 2 hr following 10 mg/kg po.

RAT

3. BIENFET, V., et al. Acta Neurol. Psychiat. Belg. *61*, 669–85 (1961)

Dose: various, sc.

The minimum dose of acepromazine causing sufficient hypotonia of feet and neck to modify the postural attitude of rats (N not given) and cause an appearance of indifference was 1 mg/kg sc. ED50 to produce a catatonic syndrome characterized by immobility, "negativism," and "passivity" was 15 mg/kg (N=50).

4. JANSSEN, P. A. J., and C. J. E. NIEMEGEERS. Arzneimittel-Forsch. *11*, 1037–43 (1961)

Dose: not given, sc.

Adult Wistar rats (N=60, 200–300 g) were pretrained in 2 daily 10-trial sessions for 5 days/week in a hurdle-box CAR (CS=buzzer, USC=50-cycle/sec, 40-v shock) to a criterion of 100% in 4 consecutive sessions. Trained rats were then tested at weekly intervals 19 hr before and 1, 5, and 25 hr after 0.02, 0.08, or 0.31 mg/kg haloperidol sc. At 1, 5, and 25 hr postdrug, the number of animals failing to avoid at least once was 12, 7, and 3, respectively, after 0.02 mg/kg, and 54, 54, and 29 after 0.31 mg/kg. Other drugs were tested, using the same test schedule and geometric doses judged of equal potency in pilot tests on 3–6 animals, and potency was determined by having trained technicians rank the graphs of escape times of each animal at each postdrug time for haloperidol and the comparison drug. Thus determined, the potency ratio of acepromazine maleate to haloperidol was 1/20.

5. LIUBIMOV, B. I. Farmakol. i Toksikol. *24*, 136–40 (1961)

Dose: various, ip.

In white rats (N=8–10/dose, 200–250 g) conditioned to jump out of a glass bell-jar (CS=bell; USC=110-v shock), the ED50 of acepromazine to abolish the motor-defensive CR was 2.05 mg/kg ip; 95% confidence limits were 1.12–3.75 mg/kg. ED50 of CPZ was 2.2 mg/kg (1.53–3.14; P=.05). UCR was not affected. The 24-hr LD50 was 140 mg/kg; that of CPZ was 155 mg/kg.

6. VENULET, J. Acta Physiol. Polon. *12*, 281–90 (1961)

Dose: 2.5–10 mg/kg sc.

An unspecified CAR (CS=bell, USC=shock, intertrial interval=30 sec, CS-USC interval=6 sec) was established in albino rats (N=10/group). The same subjects were used in repeated experiments at 1-week intervals. Control animals had 188 positive CAR/group (theoretical max=200).

In trials 30–60 min after 2.5, 5, 7.5, or 10 mg/kg acepromazine sc, CARs were 100, 56, 61, and 20, respectively. When 5 mg/kg 5-HT was given with these doses of acepromazine, positive CARs were 75, 109, 70, and 51, respectively. After pretreatment with 20 mg/kg 5-HT at ½, 1, and 4 hr before trials, 5 mg/kg acepromazine given 30 min before trials reduced positive CARs to 96, 75, and 127, respectively. The CAR was not affected by 5-HT alone.

The number of CARs in trials 30 min after 5 mg/kg acepromazine was 56. Pretreatment 4½ hr before acepromazine with 100 mg/kg iproniazid, 0.3 mg/kg amphetamine, 30 mg/kg caffeine, or 0.5 mg/kg picrotoxin (all sc and all ineffective alone) increased CAR to 133 ($P < .001$), 151 ($P = .01$), 189 ($P = .01$), or 118 ($P = .01$).

Neurology

MOUSE

7. RAEVSKII, K. S. Bull. Exptl. Biol. Med. (USSR) (English Transl.) *51*, 189–93 (1961)

Dose: various, ip.

The PD50 of acepromazine which eliminated the tonic-extensor phase of ECS (50 ma, 50 cycle/sec, for 0.2 sec at 1-hr intervals) in white mice (N not given, 24–29 g) was 32.5 mg/kg ip, the effect lasting 1.5 hr, with peak occurring at 0.5 hr. Neurological toxic dose in 50% of cases (N=10), measured by rotarod test, was 3.9 mg/kg. Therapeutic index (TD50/PD50) was 0.1.

RABBIT

8. WEBSTER, R. A. Brit. J. Pharmacol. *17*, 507–18 (1961)

Dose: 0.0125–0.025 mg/kg iv.

Local tetanus was induced in rabbits (N=7) by injection of 625 mouse minimal lethal doses of toxin into the gastrocnemius muscle, and was activated by a standard afferent stimulus. A dose of 0.019 mg/kg acepromazine iv reduced EMG-measured tetanus by 50% for 30 min. Activity was 9.4 times that of CPZ.

RAT

9. BIENFET, V., et al. Acta Neurol. Psychiat. Belg. *61*, 669–85 (1961)

Dose: 50 mg/kg po.

Administration of 50 mg/kg acepromazine po 40 min before 75 mg/kg hexobarbital ip increased sleeping time to 312% of the control value (53±1.98 min) in rats (N not given).

Physiology

DOG

10. RAPPEPORT, A. Y. Zh. Nevropatol. i Psikhiatr. *61*, 909–18 (1961)

Dose: 1–15 mg/kg im and iv.

After 3–15 mg/kg acepromazine im, the increase in heart rate of dogs (N=5, 10–23 kg) was most marked when the initial rate was low, was max at ½–1½ hr postdrug, and usually disappeared in 3–6 hr. In 1 dog, doses of 1 mg/kg iv or 10 mg/kg im were followed by bradycardia and arrhythmia lasting 2–3 days. Respiration was slowed, often 50–80%, from 15–30 min postdrug until 6–24 hr postdrug. Hypothermia (2–5 C) was max at 3 hr postdrug; temp was still below predrug levels after 6 hr. In 1 dog, temp fell 3 C after 1 mg/kg iv, and <2 C after 10 mg/kg im. Mydriasis was seen in 4 dogs, miosis in 2; pupillary changes lasted >6 hr.

RAT

11. VENULET, J. Acta Physiol. Polon. *12*, 281–90 (1961)

Dose: 0.02–25 μg/ml, in organ bath.

Contractions induced by 20 μg/ml 5-HT in the estrogen-sensitized rat uterus were inhibited by 0.02 μg/ml CPZ or acepromazine; CPZ was approx 58% less effective than acepromazine.

Contractions induced by 2.5 μg/ml 5-HT in the isolated stomach of rats were also inhibited by CPZ and acepromazine, in a final concentration of 25 μg/ml.

ACETANILIDE

Neurology

MOUSE

12. FUJIMURA, H., et al. Yakugaku Zasshi *81*, 659–63 (1961)

Dose: various, ip.

The ED50 of acetanilide to produce analgesia in mice (N not given) was 1.1 mg/10 g ip, measured by the latency of attempts to remove a clamp placed at the base of the tail. LD50 was 8.2 mg/10 g; therapeutic index was 7.45.

13. NILSEN, P. L. Acta Pharmacol. Toxicol. *18*, 10–22 (1961)

Dose: 200–400 mg/kg ip.

The percentage of mice squeaking after stimulation (16-v, 20-msec trains of square-wave pulses at 1/sec) of the tail by electrodes inserted under the skin 5–6 mm from the tip differed with strain (70% of strain I, 30 % of strain II responding), body wt (77% of 10- to 20-g, 55% of 20- to 30-g mice; N=95 and 49; .02>P>.01), and sex (65% of females, 74% of males; N=295 and 1308; .01>P>.001); in each test, the 2 parameters not under investigation were held constant. The threshold of 100 males of strain I, weighing 15–20 g, decreased significantly on a second test made within 4 hr, but subsequently remained constant; day-to-day variation was not significant.

The ED50 of acetanilide, calculated by the method of probits, to induce analgesia, defined as failure to respond to 4 consecutive stimuli of predrug threshold voltage, was 225 mg/kg ip in 15- to 20-g males of strain I (N=17-32/dose).

ACETAZOLAMIDE

2-Acetylamino-1,3,4-thiadiazole-5-sulfonamide

Neurology

MOUSE

14. GÖRES, E., et al. Acta Physiol. Acad. Sci. Hung. *19*, 95–102 (1961)

Dose: various, po.

The anticonvulsant activity of 27 compounds derived from acetazolamide or benzenesulfonamide was tested in white mice (N=10/dose, 15–25 g). The PD50 of acetazolamide against max ECS, given 75 min postdrug, was 57 mg/kg po. Other compounds showing comparable activity were 2-acetylamino-1,3,4-thiadiazole-5-(*N*-carbamoyl) sulfonamide (PD50=60 mg/kg), 2-amino-1,3,4-thiadiazole - 5 - sulfonamide (PD50=73 mg/kg), 2-(4-chlorobenzenesulfonamido)-1,3,4-thiadiazole-5-sulfonamide (PD50=63 mg/kg), 2,2′-succinyldiamino-bis-1,3,4-thiadiazole-5,5′-disulfonamide (PD50=93 mg/kg po), 4-(acetylamino) benzenesulfonamide (PD50=105 mg/kg), and 1,4-benzenedisulfonamide (PD50=62 mg/kg).

Acetazolamide was without protective effect against convulsions induced by 60–85 mg/kg pentetrazol sc or 0.8 mg/kg strychnine sc, given 75 min later. Of the other compounds tested, only one was effective against pentetrazol-induced convulsions: 120 mg/kg 2-acetylamino-1,3,4,-thiadiazole-5- (*N*,*N*-diethyl) sulfonamide po decreased the percentage of animals with convulsions from 83 to 45%. Four compounds were effective against strychnine-induced convulsions: 120 mg/kg 2-acetylamino-1,3,4-thiadiazole-5-(*N*-ethyl) sulfonamide, 2-acetylamino-1,3,4-thiadiazole-5-(*N*-methylcarbamoyl) sulfonamide, 4-(4′-aminobenzenesulfonamido) benzenesulfonamide, or 1,4-benzenedisulfonamide reduced the percentage of mice with convulsions from 45 to 10, 12, 30, and 30%, respectively. No parellelism was noted between anticonvulsant and diuretic activity; most of the compounds tested were only weakly diuretic; 2-(4-chlorobenzenesulfonamido)-1,3,4-thiadiazole-5-sulfonamide, however, had ≈7 times the diuretic activity of acetazolamide.

15. RAMWELL, P. W., and I. H. LESTER. Nature *190*, 640 (1961)

Dose: 25–500 mg/kg ip.

Sleeping time of female albino mice (N=10/group, 17–20 g) after 100 mg/kg hexobarbital ip was reduced from 31.2±3.2 min in controls to 10.3±1.7 min (P=.001) by pretreatment with 500 mg/kg acetazolamide ip 2 hr before.

PRIMATE

16. MEYER, J. S., et al. Electroencephalog. Clin. Neurophysiol. *13*, 762–75 (1961)

Dose: 15–250 mg/kg iv.

Rhesus monkeys (N=26) were anesthetized with ether during implantation of cortical electrodes and electrodes for recording of cortical

oxygen tension, cortical CO_2 tension, and cortical and arterial sodium and potassium activities; cortical blood flow was measured with a thermistor placed on the cortical surface. The animals were then immobilized with (+)-tubocurarine and given artificial ventilation. Seizures were induced by strychnine sulfate iv, 200,000 units of penicillin topically to the cortex, (+)-tubocurarine topically to the cortex, or hypoglycemia. Doses of 15–25 mg/kg acetazolamide iv decreased spike amplitude, caused a transient increase in arterial pH, increased cortical blood flow and arterial brain CO_2 tension; deep and surface cortical pH decreased. The effects were similar to those seen after CO_2 inhalation; 250 mg/kg acetazolamide, which increased brain pH, was less effective than CO_2.

ACETYLCHOLINE

Behavior

BIRD

17. DESHPANDE, V. R., et al. Brit. J. Pharmacol. *17*, 7–11 (1961)

Dose: not given, ip.

Ach was administered to pigeons (N not given, 250–300 g) housed in separate wire mesh cages with no food or water; criterion of positive response was ≥10 pecking responses during 30 min. Same subjects were used in other trials at 4-day intervals. No positive pecking response was induced in the treated pigeons.

MOUSE

18. NISHIOKA, T. Kagoshima Daigaku Igaku Zasshi *12*, 112–56 (1961)

Dose: 0.01 mg/g sc.

Avg swimming time to exhaustion for mice (N=5) at 15–22 C was 42 min; avg time to recovery (gross observation) was 1 hr. Thirty min after 0.001–0.008 mg/g *Trimeresurus flavoviridis* venom (T. venom) sc (N=2/dose), avg swimming time was 2½ hr after 0.001–0.002 mg/g, 1 hr after 0.003 mg/g, and 23–40 min after larger doses. Recovery times ranged from ½–4½ hr.

Avg swimming time 30 min after 0.01 mg/g Ach sc (N=3) was 42 min; recovery time was 107 min. In mice (N=3) pretreated with 0.002 mg/g T. venom, avg swimming time 30 min after 0.01 mg/g Ach was 85 min; recovery time was 130 min.

Neurology

MOUSE

19. NISHIOKA, T. Kagoshima Daigaku Igaku Zasshi *12*, 112–56 (1961)

Dose: 0.03–0.3 mg/g sc.

In control mice (N=10) with needle electrodes in the ears, lethal voltage was 25 v for 1 sec. Tested ½–24 hr after 0.001–0.004 mg/g *Trimeresurus flavoviridis* venom (T. venom) sc, lethal voltage was 40->130 v (N=4/dose); lethal voltage 3 hr after 0.002 mg/g was 110 v.

Lethal voltage of 25 v after 0.03–0.3 mg/g Ach sc (N=3) was changed to 20->130 v by pretreatment 3 hr before with 0.002 mg/g T. venom.

RABBIT

20. DENISENKO, P. P. Sechenov Physiol. J. USSR (English Transl.) *47*, 124–31 (1961)

Dose: 0.1–50 μg/kg iv.

In rabbits (N not given, 3–4 kg) with electrodes implanted in temporal and occipital cortex, thalamus, and hypothalamus, injection of 0.1–50 μg/kg Ach iv produced behavorial and EEG arousal, tremor, and convulsions for a brief interval, followed by pronounced depression of electrical activity. EEG changes were characterized by increased amplitude and number of fast rhythms and a diminution or disappearance of high amplitude slow waves.

Physiology

AMPHIBIAN

21. PETKOV, W. Arzneimittel-Forsch. *11*, 288–95 (1961)

Dose: 1:5,000,000–1:100,000 solution, in muscle bath.

Immediate, rapid contraction was induced in isolated rectus muscles of frogs (N=4-20/group) after application of 1:200,000 solution of Ach; recovery after rinsing was also immediate. Ach was 500–1000 times stronger in activity than the dried extract of *Panax ginseng* when tested on the same muscles. When Ach and ginseng were administered consecutively in threshold concentrations, or in threshold concentration of Ach and optimal concentration of ginseng, synergism was present; opti-

mally effective concentrations of the 2 drugs, given seriatim, induced only partial summation or inhibition. Ach-induced contraction was blocked or prevented by 1:150,000 tubocurarine.

INVERTEBRATE

22. PETKOV, W. Arzneimittel-Forsch. *11*, 288–95 (1961)

Dose: 1:100,000 solution, in muscle bath.

Contractions induced in the denervated back muscles of leeches (N=12) by 1:100,000 Ach were increased 4- to 5-fold in amplitude by 1:100,000 physostigmine salicylate; they were not altered by 1:2000–1:200 solutions of the dried extract of *Panax ginseng*. Ginseng alone or with physostigmine did not induce contractions of the muscle.

MOUSE

23. NISHIOKA, T. Kagoshima Daigaku Igaku Zasshi *12*, 112–56 (1961)

Dose: 0.3–2 mg/g sc.

The LD50 of *Trimeresurus flavoviridis* venom (T. venom) in mice was 0.004 mg/g sc. Mice (N=5) given 0.3–2 mg/g Ach sc died in 6–13 min. In mice pretreated with 0.002 mg/g T. venom, survival time after these doses of Ach was 8–110 min.

RABBIT

24. PETKOV, W. Arzneimittel-Forsch. *11*, 288–95 (1961)

Dose: 1:10,000,000–1:200,000 solution, in muscle bath.

Contractions induced in isolated loops of rabbit intestine by Ach (1:10,000,000–1:200,000) were immediately antagonized by ginseng (1:1350–1:600). Pretreatment with 1:1000 ginseng inhibited Ach-induced contractions. Summation of effects was seen after combined threshold concentrations of Ach and ginseng.

ACETYL LYSERGIC ACID DIETHYLAMIDE

Neurology

PRIMATE

25. MONROE, R. R., and R. G. HEATH. J. Neuropsychiat. *3*, 75–82 (1961)

Dose: 140–500 μg/kg, route not given.

Electrodes were stereotaxically implanted (with X-ray confirmation) over the frontal and occipital cortex and in the septal, caudate, and hippocampal regions of *Macaca mulatta* monkeys (N=6). The animals were studied over a period of 1–3 months in 3–20 separate experiments using different drugs; sufficient time (≤48 hr) elapsed between experiments to allow EEG to return to normal. The animals were lightly restrained during each experiment, and behavior ratings were made while electrical activity of brain was being recorded.

Three animals became agitated after 140–500 μg/kg (±)-acetyl lysergic acid diethylamide, but there was no evidence of catatonic behavior (defined as passive flexion and unresponsiveness to external stimuli, with the animal obviously awake). Paroxysmal activity of 12–15/sec appeared in the frontal, hippocampal, and occasionally in the parietal leads, but only minimal changes occurred in the septal leads.

ACETYLSALICYLIC ACID

Behavior

DOG

26. VOROBIOVA, T. M. Fiziol. Zh. Akad. Nauk Ukr. RSR *7*, 24–31 (1961)

Dose: 0.5–5 mg, by injection.

A salivary reflex was established in dogs (N not given) by classical methods (CS_+=light, bell, electric hammer, rattle; CS_-=weak light; UCS not stated). Injection of 1 mg acetylsalicylic acid daily for 5 days 1 hr before testing caused a marked increase in CR_+ on the first day of drug administration, without loss of differentiation. On subsequent days CR_+ returned progressively to predrug levels at day 4 and then fell somewhat below them on days 5 and 6.

RAT

27. WEISS, B., and V. G. LATIES. J. Pharmacol. Exptl. Therap. *131*, 120–9 (1961)

Dose: 125–250 mg/kg po.

Wistar and Holtzman albino rats (N=10) were trained to press a bar to reduce shock which increased every 2 sec (0.07–0.65 ma in 25 discrete and equal steps, 60 cycle/sec). When the shock level maintained by the animals was stable, the rats were given 125 or 250 mg/kg

acetylsalicylic acid by stomach tube and tested over a 130-min period beginning 60 min postinjection. The higher dose increased the median shock levels maintained by the animals compared with saline controls ($P<.05$).

In a Skinner box, rats (N=7) were trained for 2 hr to escape shock (0.64 ma, 60 cycle/sec, 2/min) by pressing a lever. The animals were tested twice for a 2-hr period beginning 1 hr after 250 mg/kg acetylsalicylic acid; no effect was seen.

After 60 hr of training on a drl 20-sec schedule for water reinforcement, rats (N=3) were given three 2-hr tests 1 hr after saline or 125 or 250 mg/kg acetylsalicylic acid. Both doses significantly decreased the total number of responses but did not change IRT distributions. In rats (N=6) pretrained on a VI schedule of 120 sec for water reinforcement and tested for a 2-hr period beginning 1 hr after 125 or 250 mg/kg acetylsalicylic acid, the higher dose decreased response rate from 4.1/min for saline controls to 2.2/min ($P=.01$). Treatment variance for both doses was linear ($P<.01$).

Neurology

DOG

28. BRAUN, C., et al. J. Physiol. *155*, 13P–14P (1961)

Dose: 25–50 mg/kg iv.

In dogs (N=11) given 80 mg/kg chloralose iv, intra-arterial injection of 1.2 μg bradykinin produced vocalization, hyperpnea, and vasomotor changes. A dose of 25–50 mg/kg sodium acetylsalicylate iv blocked the response completely in 4 and partially in 5 dogs for 45–60 min.

GUINEA PIG

29. FROMMEL, E., et al. Arch. Intern Pharmacodyn. *130*, 235–59 (1961)

Dose: 100 mg/kg po.

The pain threshold (voltage of 40-cycle/sec, 0.5-sec square-wave pulses to the dental pulp) of guinea pigs (N=5) was elevated 16% by 100 mg/kg acetylsalicylic acid po. The analgesic effect of 100 mg/kg was not potentiated by 25–200 mg/kg 3-(*N*-pyrrolidino)butyranilide po.

MOUSE

30. BASTIAN, J. W. Arch. Intern. Pharmacodyn. *133*, 347–64 (1961)

Dose: various, po.

Spontaneous activity of CFW mice (N=15/dose, 17–24 g) was measured in a tilting cage during a 15-min period ending 30, 60, or 120 min after various doses of acetylsalicylic acid.

Ataxia was then evaluated by rating the animals on ability to descend a vertical polished rod (½-inch diam, 3 feet high), and rectal temp was measured. Pentetrazol was then infused at 2 mg/min iv until death or for 180 sec; latency of seizures, presence or absence of a tonic-extensor phase, and time to death were recorded. For untreated controls (N=193 groups of 5), the motor activity count was 11–38, ataxia score was 0–0.3, body temp was 99.2–102.0 F, latency of pentetrazol seizures was 37–65 sec, blocking of extensor tonus was 0%, and the time to death was 46–86 sec (95% confidence levels). After 400 mg/kg acetylsalicylic acid po, scores on the 6 measures were 10,* 0.2, 99.6 F, 45 sec, 20%,* 66 sec, respectively, at 60 min postdrug, the time of peak action. (*$P<.05$).

31. KISSEL, J. W., et al. J. Pharmacol. Exptl. Therap. *134*, 332–40 (1961)

Dose: various, sc.

Swiss-Webster mice (N=10–20/dose) were given 2.5 mg/kg phenylquinone ip at the peak-effect time after various doses of acetylsalicylic acid. Writhing episodes were counted for 10 min. The dose of acetylsalicylic acid to reduce writhing by 50% was 20 mg/kg sc at a peak-activity time of 30 min.

32. NILSEN, P. L. Acta Pharmacol. Toxicol. *18*, 10–22 (1961)

Dose: 250–500 mg/kg ip.

The percentage of mice squeaking after stimulation (16-v, 20-msec trains of square-wave pulses at 1/sec) of the tail by electrodes inserted under the skin 5–6 mm from the tip differed with strain (70% of strain I, 30% of strain II responding), body wt (77% of 10- to 20-g, 55% of 20- to 30-g mice; N=95 and 49; $.02>P>.01$), and sex (65% of females, 74% of males; N=295 and 1308; $.01>P>.001$); in

each test, the 2 parameters not under investigation were held constant. The threshold of 100 males of strain I, weighing 15–20 g, decreased significantly on a second test made within 4 hr, but subsequently remained constant; day-to-day variation was not significant.

The ED50 of acetylsalicylic acid, calculated by the method of probits, to induce analgesia, defined as failure to respond to 4 consecutive stimuli of predrug threshold voltage, was 580 mg/kg ip in 15- to 20-g males of strain I (N=135).

RAT

33. ALEXANDER, K., and G. SCHMITT. Arch Intern. Pharmacodyn. *132*, 126–38 (1961)

Dose: 10 mg/kv iv.

The CD50 of cocaine in white rats (N=25, 100–150 g), deprived of food for 12 hr before tests, was increased from 9.3 to 10.9 mg/kg iv by pretreatment 15 min before cocaine with 10 mg/kg acetylsalicylic acid iv.

34. SILVESTRINI, B., and C. POZZATTI. Brit. J. Pharmacol. *16*, 209–17 (1961)

Dose: 10–20 mg/kg sc.

Inflammation of the paw was produced in Long-Evans rats (N=5–20/dose, 150–200 g) by injection of 0.1 ml 20% brewer's yeast; pressure was applied to the inflamed area and increased at 20 mm Hg/sec; endpoint was flight reaction (struggle). The pain threshold was significantly increased at 30–90 min after 20 mg/kg acetylsalicylic acid sc ($.01>P>.001$); max analgesia occurred at 30 min postdrug.

Physiology

RAT

35. SILVESTRINI, B., and C. POZZATTI. Brit. J. Pharmacol. *16*, 209–17 (1961)

Dose: 60–120 mg/kg sc and po.

In Long-Evans rats (N=20-29/dose, 150–200 g) with approx the same limb vol, edema was induced by injection of brewer's yeast into the paw. Treatment with 60 or 120 mg/kg acetylsalicylic acid sc reduced the limb vol 0.03 and 0.084 ml, respectively, at 2 hr and 0 and 0.067 ml at 24 hr. A dose of 100 mg/kg po had an antipyretic effect in rats with yeast-induced hyperthermia.

ACRINOL

6,9-Diamino-2-ethoxyacridine lactate monohydrate

Behavior

MOUSE

36. NISHIOKA, T. Kagoshima Daigaku Igaku Zasshi *12*, 112–56 (1961)

Dose: 0.1 mg/g sc.

Avg swimming time to exhaustion for mice (N=5) at 15–22 C was 42 min; avg time to recovery (gross observation) was 1 hr. Thirty min after 0.001–0.008 mg/g *Trimeresurus flavoviridis* venom (T. venom) sc (N=2/dose), avg swimming time was 2½ hr after 0.001–0.002 mg/g, 1 hr after 0.003 mg/g, and 23–40 min after larger doses. Recovery times ranged from ½-4½ hr.

Avg swimming time 30 min after 0.1 mg/g acrinol sc (N=3) was 15 min; recovery time was 2 hr. In mice (N=3) pretreated with 0.002 mg/g T. venom, avg swimming time 30 min after 0.1 mg/g acrinol was 62 min; recovery time was 2 hr.

Physiology

INVERTEBRATE

37. NISHIOKA, T. Kagoshima Daigaku Igaku Zasshi *12*, 112–56 (1961)

Dose: 0.025% solution, in bath.

Ten ml of 0.001–0.015% solution of venom from *Trimeresurus flavoviridis* (T. venom) was added to a vessel containing *Rhynchelmis orientalis* (N=5/container). After 3-hour exposure, none died; at 12 hr, all exposed to the 0.015% solution were dead; at 24 hr, 2 of those exposed to the 0.005% solution were dead. Higher concentrations (0.025–0.05%) were lethal in ½–3 hr. After exposure to solutions of T. venom which had been digested for 1 hr with a proteolytic enzyme, no animals were dead at 3 hr, 5/5 were dead at 24 hr in 0.003–0.125% solutions, 3/5 in 0.025–0.05% solution.

After immersion in 10 ml of 0.025% acrinol, 3 worms (R.O.) were dead at 20 min and 5/5 at 30–60 min. When the acrinol solution was added after 30-min exposure to 0.001, 0.003, 0.005, or 0.01% T. venom, death of 5/5 animals occurred at 60, 60, 60, and 90 min, respectively. When the acrinol solution was

added after 30-min exposure to 0.002, 0.006, 0.01, or 0.02% digested venom, 5/5 were dead at 60 min.

MOUSE

38. NISHIOKA, T. Kagoshima Daigaku Igaku Zasshi *12*, 112–56 (1961)

Dose: 0.5–3 mg/g sc.

The LD50 of *Trimeresurus flavoviridis* venom (T. venom) in mice was 0.004 mg/g sc. Mice (N=3) given 1.5–3 mg/g acrinol sc died in 3½–6 hr; those (N=2) given 0.5–1 mg/g survived for 24 hr. In mice pretreated with 0.002 mg/g T. venom, survival time after 1–3 mg/g acrinol was 5–24 hr; a dose of 0.5 mg/g was not lethal.

ADENOSINE

Neurology

RAT

39. BUDAY, P. V., et al. J. Pharm. Pharmacol. *13*, 290–9 (1961)

Dose: 25–500 μg, intraventricular.

Intraventricular injection of 25–500 μg adenosine into conscious albino rats (N=6/dose, 55–140 g) elicited an akinetic state and weakness.

Physiology

AMPHIBIAN

40. BUDAY, P. V., et al. J. Pharm. Pharmacol. *13*, 290–9 (1961)

Dose: 8.26×10^{-7}–3.31×10^{-5} M, by perfusion.

Hearts from *Rana pipiens* frogs (N not given, 7.5–8.8 cm) were perfused *in situ* with modified Howell-Ringer solution (pH=7.2; temp=24–27 C). Addition of adenosine, at concentrations of 8.26×10^{-7} to 3.31×10^{-5} M, produced bradycardia and diastolic arrest in the higher concentrations, with minor enhancement of cardiac excursions. Concomitant perfusion with 3.0×10^{-5} M methylene blue inhibited the bradycardia induced by adenosine.

The cardio-acceleration induced by 5.46×10^{-9} M (–)-epinephrine HCl or 6.26×10^{-9} M (–)-norepinephrine bitartrate was readily inhibited (7–100%) by concomitant perfusion with 3.37×10^{-5} M adenosine. The cardio-depressant property of 7.37×10^{-4} M pilocarpine nitrate was not affected by concomitant perfusion with 3.31×10^{-5} M adenosine.

RAT

41. BUDAY, P. V., et al. J. Pharm. Pharmacol. *13*, 290–9 (1961)

Dose: 7.48×10^{-5}–2.24×10^{-4} M.

In isolated uteri from albino rats (120–235 g) pretreated with 50 μg/100 g diethylstilbestrol sc at 2- to 24-hr intervals for 72 hr, a concentration of 7.48×10^{-5} or 2.24×10^{-4} M adenosine had no uteromotor effect.

ADENOSINE MONOPHOSPHATE

Physiology

INVERTEBRATE

42. BUDAY, P. V., et al. J. Pharm. Pharmacol. *13*, 290–9 (1961)

Dose: 2.24×10^{-4}–1.34×10^{-3}M, in organ bath.

Isotonic contractions of isolated heart ventricles of the lamellibranch clam, *Venus mercenaria*, were gradually inhibited and arrested in diastole by concentrations of 2.24×10^{-4}–1.34×10^{-3} M adenosine-5′-monophosphate (AMP). No tachyphylaxis was noted. The addition of 4.84×10^{-5} M benzoquinonium chloride, 1 min before AMP, delayed or prevented inhibition.

RAT

43. BUDAY, P. V., et al. J. Pharm. Pharmacol. *13*, 290–9 (1961)

Dose: 7.48×10^{-5}–2.24×10^{-4} M, in organ bath.

In isolated uteri from albino rats (120–235 g) pretreated with 50 μg/100 g diethylstilbestrol sc at 2- to 24-hr intervals for 72 hr, a concentration of 7.48×10^{-5} or 2.24×10^{-4} M adenosine-5′-monophosphate had no uteromotor effect.

ADENOSINE TRIPHOSPHATE

Behavior

RAT

44. DA SILVA, A. B., and J. A. LEITAO. Med. Contemp. *79*, 311–42 (1961)

Dose: 1–2 mg ip.

When wt equivalent to 4% of body wt was attached to the tails of white rats (N=5, ≈200 g) previously deprived of food for 24 hr, avg swimming time in a bath (90 x 60 x 60 cm)

at 19 C was 13.6±1.86 min. Five min after 1 mg ATP ip, swimming time was 22.4±5.46 min ($P<.001$). After a 2½-hr rest, controls swam 13.6±1.86 min and glucose-treated animals swam 22.2±2.54 min. ($.01>P>.001$). In second test, controls swam 13.8±2.34 min; after 2 mg ATP, they swam 28±26.3 min ($.01>P>.001$). After the 2½-hr rest period, controls swam 13.4±1.46 min and ATP-treated animals swam 26.8±15.34 min ($.02>P>.01$). Swimming times after the 2 doses of ATP did not differ significantly.

Neurology

RABBIT

45. ARUSHANYAN, E. B. Issled. po Farmakol. Retikulyarnoi Formatsii i Sinapticheskoi Peredachi, 1-yi (Pervyi) Leningr. Med. Inst. 282–6 (1961)

Dose: 1.5–3 mg/kg iv.

The threshold of electrical stimulation (0.1–4 ma, 1–2 sec) causing flexion of the hindleg in rabbits (N not given) was 1.6 ma; at 2, 3, and 6 hr after 8–12 mg/kg morphine iv, it was 3.1, 3.0 and 2.1 ma, respectively. Injection of 1.5–3 mg/kg adenosine triphosphate iv 1 hr after morphine antagonized the analgesia: the pain threshold at 2, 3, and 6 hr after morphine was 2.3, 2.0, and 1.5 ma, respectively.

The number of subthreshold electrical stimuli (parameters not given) required to induce the flexor reflex was increased by 2 mg/kg morphine and returned to normal in 90 min; after pretreatment with 2 mg/kg adenosine triphosphate 45–60 min before morphine, the predrug level was attained in 25 min.

RAT

46. BUDAY, P. V., et al. J. Pharm. Pharmacol. *13*, 290–9 (1961)

Dose: 25–1500 μg, intraventricular.

Intraventricular injection of 1000 or 1500 μg ATP into conscious albino rats (N=6/dose, 55–140 g) elicited severe, generally unilateral, clonic-tonic convulsions lasting 15–90 sec and at times characterized by a spiral body movement. This stage was followed by anergia or akinesis with concomitant asthenia of the limbs lasting 4–26 min. After 25–500 μg, only the akinetic state and weakness were observed.

Physiology

AMPHIBIAN

47. BUDAY, P. V., et al. J. Pharm. Pharmacol. *13*, 290–9 (1961)

Dose: 4.13×10^{-7}–3.31×10^{-5} M, by perfusion.

Hearts from *Rana pipiens* frogs (N not given, 7.5–8.8 cm) were perfused *in situ* with modified Howell-Ringer solution (pH=7.2; temp=24–27 C). Addition of ATP, to a concentration of 8.26×10^{-7} M, increased systolic force and slowed the heart rate. A profound but transitory heart block was seen after 8.26×10^{-6} to 3.31×10^{-5} M.

Concomitant perfusion with a just subthreshold concentration of (–)-epinephrine HCl (1.09×10^{-12} M) or (–)-norepinephrine bitartrate (1.25×10^{-11} M) and a threshold concentration of ATP (4.13×10^{-7} M) failed to show any potentiation of amplitude (N=6).

The depressant effect of 7.37×10^{-4} M pilocarpine nitrate on the heart was obliterated transiently by ATP in concentrations of 8.26×10^{-6} to 3.31×10^{-5} M.

Concomitant perfusion with 3.0×10^{-5} M methylene blue inhibited the bradycardia but did not suppress the inotropic effect of 8.26×10^{-6} M ATP (N=7).

INVERTEBRATE

48. BUDAY, P. V., et al. J. Pharm. Pharmacol. *13*, 290–9 (1961)

Dose: 4.84×10^{-5}–1.34×10^{-3} M, in organ bath.

Isotonic contractions of isolated heart ventricles of the lamellibranch clam, *Venus mercenaria*, were gradually inhibited and arrested in diastole by concentrations of 2.24×10^{-4}–1.34×10^{-3} M ATP. For complete inhibition within 1 min, 6.72×10^{-4} M was required. No tachyphylaxis was noted. The addition of 4.84×10^{-5} M benzoquinonium chloride, 1 min before ATP, delayed or prevented inhibition. The presence of 1.18×10^{-6} M 5-HT creatinine sulfate completely protected against the action of ATP in 4/5 hearts.

RAT

49. BUDAY, P. V., et al. J. Pharm. Pharmacol. *13*, 290–9 (1961)

Dose: 2.24×10^{-5}–2.24×10^{-4} M, in organ bath.

In isolated uteri from albino rats (120–235 g) pretreated with 50 μg/100 g diethylstilbestrol