DOPAMINE AND NEUROENDOCRINE ACTIVE SUBSTANCES

Edited by
EMILIO DEL POZO
EDWARD FLÜCKIGER

Dopamine and Neuroendocrine Active Substances

Proceedings of the First Symposium of the European Neuroendocrine Association (E.N.E.A.) Basle, Switzerland, March 4-7, 1984

Edited by

Emilio del Pozo
Clinical Research
SANDOZ
Basle, Switzerland

Edward Flückiger
Preclinical Research
SANDOZ
Basle, Switzerland

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Contributors

L. F. Agnati *Department of Histology and Hormone Laboratory, Karolinska Institutet, Stockholm, Sweden.*
J. Alba-Lopez *Experimental Therapeutics Department, Sandoz Limited, Basle, Switzerland.*
J. Anderson *University of Virginia School of Medicine, Charlottesville, Virginia 22908, USA.*
K. Andersson *Department of Histology and Hormone Laboratory, Karolinska Institutet, Stockholm, Sweden.*
B. Bernardi *Department of Histology and Hormone Laboratory, Karolinska Institutet, Stockholm, Sweden.*
R. M. Blizzard *University of Virginia, Charlottesville, Virginia 22908, USA.*
D. B. Calne *Division of Neurology, University of British Columbia, Vancouver BC, Canada.*
T. Caraceni *Department of Neurology, Istituto Neurologico 'C Besta', Via Celoria 11, 20133 Milan, Italy.*
F. Cavagnini *First Medical Clinic, University of Milan, 20122 Milan, Italy.*
S. Cella *Department of Pharmacology, University of Milan, 20129 Milan, Italy.*
S. E. Christensen *Second University Clinic of Internal Medicine, Aarhus Kommunehospital, DK-8000 Aarhus C, Denmark.*
D. Cocchi *Department of Pharmacology, University of Milan, 20129 Milan, Italy.*
M. Cronin *University of Virginia School of Medicine, Charlottesville, Virginia 22908, USA.*
C. Dieguez *Department of Medicine, Welsh National School of Medicine, Heath Park, Cardiff CF4 4XN, UK.*
J. Djiane *Laboratoire de Physiologie de la Lactation, I.N.R.A., 78350 Jouy-en-Josas, France.*
P. Donatsch *Preclinical Research Department, Sandoz Limited, CH-4002 Basle, Switzerland.*
E. Dupont *University Department of Neurology, Aarhus Kommunehospital, DK-8000 Aarhus C, Denmark.*
P. Eneroth *Department of Histology and Hormone Laboratory, Karolinska Institutet, Stockholm, Sweden.*
W. S. Evans *University of Virginia, Charlottesville, Virginia 22908, USA.*
P. Falaschi *Medical Clinic V, University of Rome, 00100 Rome, Italy.*
B. de Fine Olivarius *University Department of Neurology, Aarhus Kommunehospital, DK-8000 Aarhus C, Denmark.*
S. M. Foord *Department of Medicine, Welsh National School of Medicine, Heath Park, Cardiff CF4 4XN, UK.*
L. A. Frohman *University of Cincinnati, Cincinatti, OH 45267, USA.*

R. Furlanetto *The Children's Hospital of Philadelphia, PA 19104, USA.*
K. Fuxe *Department of Histology and Hormone Laboratory, Karolinska Institutet, Stockholm, Sweden.*
P. Giovannini *Department of Neurology, Istituto Neurologico 'C Besta', Via Celoria 11, 20133 Milan, Italy.*
M. Goldstein *Department of Histology and Hormone Laboratory, Karolinska Institutet, Stockholm, Sweden.*
A. Gómez-Pan *Endocrinology Department, CNEQ Pabellon 8, Faculty of Medicine, 28040 Madrid, Spain.*
A. Guitelman *Department of Endocrinology, Hospital Alvares, Buenos Aires, Argentina.*
J. A. Gustafsson *Department of Histology and Hormone Laboratory, Karolinska Institutet, Stockholm, Sweden.*
R. Hall *Department of Medicine, Welsh National School of Medicine, Heath Park, Cardiff CF4 4XN, UK.*
A. Harfstrand *Department of Histology and Hormone Laboratory, Karolinska Institutet, Stockholm, Sweden.*
P. E. Harris *Department of Medicine, Welsh National School of Medicine, Heath Park, Cardiff CF4 4XN, UK.*
E. Hewlett *University of Virginia School of Medicine, Charlottesville, Virginia 22908, USA.*
C. Invitti *First Medical Clinic, University of Milan, 20122 Milan, Italy.*
P. B. Jorgensen *University Department of Neurology, Aarhus Kommunehospital, DK-8000 Aarhus C, Denmark.*
D. L. Kaiser *University of Virginia, Charlottesville, VA 22908, USA.*
M. Katoh *Laboratory of Molecular Endocrinology, Royal Victoria Hospital, Montreal, Quebec H3A 1A1, Canada.*
P. A. Kelly *Laboratory of Molecular Endocrinology, Royal Victoria Hospital, Montreal, Quebec H3A 1A1, Canada.*
D. Koritnik *Bowman Gray School of Medicine, Winston-Salem, North Carolina 27103, USA.*
A. Laihinen *Department of Neurology, University of Turku, SF-20520 Turku 52, Finland.*
S. W. J. Lamberts *Department of Medicine, Erasmus University, Rotterdam, The Netherlands.*
R. Landgraf, *Medizinische Klinik Innenstadt, University of Munich, 8000 Munich 2, FRG.*
P. A. LeWitt *Department of Neurology, Lafayette Clinic, 951 E Lafayette, Detroit, MI 48207, USA.*
G. Leyendecker *Department of Obstetrics and Gynecology, University of Bonn, 53 Bonn-Venusberg, FRG.*
V. Locatelli *Department of Pharmacology, University of Milan, 20129 Milan, Italy.*
P. J. Lowry *Protein Hormone Unit, St Bartholomew's Centre for Clinical Research, London EC1A 7BE, UK.*
L. Martini *Department of Endocriniology, University of Milan, 20129 Milan, Italy.*
J. H. Mendelson *Alcohol and Drug Abuse Research Center, Harvard Medical School-McLean Hospital, 115 Mill Street, Belmont, MA 02178, USA.*
N. K. Mello *Alcohol and Drug Abuse Research Center, Harvard Medical School-McLean Hospital, 115 Mill Street, Belmont, MA 02178, USA.*

D. Müller *Experimetal Therapeutics Department, Sandoz Limited, Basle, Switzerland.*
E. E. Müller *Department of Pharmacology, University of Milan, 20129 Milan, Italy.*
O. A. Müller *Medizinische Klinik Innenstadt, University of Munich, 8000 Munich 2, FRG.*
A. Neil *Department of Pharmacology, Uppsala University, Biomedical Center, Box 573, S-751 23 Uppsala, Sweden.*
R. P. Newman, *Dent Neurologic Institute, Buffalo, NR, USA.*
F. Nyberg *Department of Pharmacology, Uppsala University, Biomedical Center, Box 573, S-751 23 Uppsala, Sweden.*
R. Oeckler *Neurochirurgische Klinik Grosshadern, Frauenklinik, University of Munich, 8000 Munich 2, FRG.*
H. Orskov *Institute of Experimental Clinical Research, Aarhus Kommunehospital, DK-8000 Aarhus C, Denmark.*
E. Parati *Department of Neurology, Istituto Neurologico, 'C Besta', Via Celoria 11, 20133 Milan, Italy.*
J. R. Peters *Department of Medicine, Welsh National School of Medicine, Heath Park, Cardiff CF4 4XN, UK.*
E. Polak *Department of Endocrinology, Hospital Alvares, Buenos Aires, Argentina.*
E. Del Pozo *Experimental Therapeutics Department, Sandoz Limited, CH-4002 Basle, Switzerland.*
B. P. Richardson *Preclinical Research Department, Sandoz Limited, CH-4002 Basle, Switzerland.*
U. K. Rinne *Department of Neurology, University of Turku, SF-20520 Turku 52, Finland.*
J. Rivier *Peptide Biology Laboratory, The Salk Institute, San Diego, CA 92138-9216, USA.*
H. K. Rjosk *Frauenklinik, University of Munich, 8000 Munich 2, FRG.*
A. Rocco *Medical Clinic V, University of Rome, 00100 Rome, Italy.*
M. D. Rodriguez-Arnao, *Endocrinology Service, Hospital Provinical, 28009 Madrid, Spain.*
A. D. Rogol *University of Virginia, Charlottesville, VA 22908, USA.*
M. Rosa *Medical Clinic V, University of Rome, 00100 Rome, Italy.*
M. F. Scanlon *Department of Medicine, Welsh National School of Medicine, Heath Park, Cardiff CF4 4XN, UK.*
J. Schopohl *Medizinische Klinik Innenstadt, University of Munich, 8000 Munich 2, FRG.*
G. Scigliano *Department of Neurology, Istituto Neurologico, 'C Besta', Via Celoria 11, 20133 Milan, Italy.*
G. K. Stalla *Medizinische Klinik Innenstadt, University of Munich, 8000 Munich 2, FRG.*
L. Terenius *Department of Pharmacology, Uppsala University, Biomedical Center, Box 573, S-751 23 Uppsala, Sweden.*
M. O. Thorner *University of Virginia, Charlottesville, VA 22908, USA.*
G. Tolis *Division of Endocrinology, Hippokrateion Hospital, 115 27 Athens, Greece.*
W. Vale *Peptide Biology Laboratory, The Salk Institute, San Diego, CA 92138-9216, USA.*

W. Vale *Department of Histology and Hormone Laboratory, Karolinska Institutet, Stockholm, Sweden.*
M. L. Vance *University of Virginia, Charlottesville, VA 22908, USA.*
K. Von Werder *Medizinische Klinik Innenstadt, University of Munich, 8000 Munich 2, FRG.*
L. Wildt *Department of Obstetrics and Gynecology, University of Bonn, 53 Bonn-Venusberg, FRG.*
M. Wills *Department of Medicine, University of Virginia School of Medicine, Charlottesville, Virginia, USA.*
Z. Y. Yu *Department of Histology and Hormone Laboratory, Karolinska Institutet, Stockholm, Sweden.*
A. Yotis *Division of Endocrinology, Hippokrateion Hospital, 115 27 Athens, Greece.*

PREFACE

This volume comprises the invited reports delivered at the 1st Meeting of the European Neuroendocrine Association (E.N.E.A.) in Basel (4-7, March 1984). The reports present neuroendocrine advances both in laboratory work and at the clinical level, and they cover a wide spectrum of physiological, pathophysiological and pharmacological interests. This encompasses neurohistological aspects of the hypothalamo-pituitary axis, neuromodulators, neurotransmitters, as well as aspects of receptors on hormonal target cells. Rapid progress in separate fields have contributed to the present day understanding of neuroendocrine mechanisms, from the molecular level to the organismic level. It was therefore felt necessary to bring together these different but interrelated areas of work under the common denominator of the European Neuroendocrine Association. It was hoped that such a meeting would facilitate a stimulating exchange of knowledge and speculations. During the E.N.E.A. Meeting the positive aspects of such an interdisciplinary approach as this conference provided were felt very strongly by many participants. In reading the chapters of this volume this impression is revived.

A collection of further reports with a heavier bias towards neurological aspects and problems will be published in a separate volume.

E. del Pozo E. Flückiger

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PHARMACOLOGY OF DOPAMINOMIMETIC DRUGS

E. Flückiger

Pharmaceutical Division, Preclinical Research
SANDOZ LTD.,
CH-4002 Basel, Switzerland

INTRODUCTION

It seems of interest to note that dopamine pharmacology developed in two distinct phases. In the fifties and sixties it was the aspect of dopamine antagonism (neuroleptics) and now in the seventies and eighties it is dopamine receptor agonists which attract so much attention. Both phases were successfully opened by phenomenological pharmacology, receptor pharmacology being a more recent chapter.

Although it was recognized already in the fifties that neuroleptics (dopamine antagonists) have endocrine effects (e.g. galactorrhea in patients treated with chlorpromazine (43), experimental induction of lactation in rabbits with the same drug (2), this had little consequences in pharmacological endocrinology, with the notable exception of Sulman's attempt to select prolactin stimulating drugs lacking central sedative effects (for review: see 40). Shelesnyak in an entirely different context but simultaneously discovered and explored the prolactin secretion inhibitory property of ergot alkaloids (e.g. 38; 39; 26), again with no immediate echo in pharmacological endocrinology. The scene became activated at the beginning of the seventies when bromocriptine, which had been selected and developed for clinical use as a prolactin secretion inhibitor pure and simple (15; 12) was demonstrated in the rat to have central dopamine agonist activity (20; 24; 8), to be of benefit in M. Parkinson patients (4, 5) and to lower circulating growth hormone levels in acromegalic patients (28). Both these effects were explained to be related to its direct dopaminomimetic property, and a few years later it became certain that prolactin secretion inhibition also was due to this property (29). In the past ten years the pharmacology of do-

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paminomimetics has developed in various directions, the major ones being: receptor characterization (by biochemical, biophysical, physico-chemical, anatomical, behavioural criteria), target cell physiology, drug chemistry.

DOPAMINE RECEPTORS

Experimental evidence indicates that dopamine receptors function in many regulatory systems and that they occur in various subtypes, differing not only by anatomic criteria (autoreceptors, pre- and postsynaptic receptors) but also by biochemical and functional criteria (such as being linked to an adenylate cyclase system in a inhibitory or excitatory way, or not being linked to adenylate cyclase) or by physico-chemical criteria (radioligand studies). Dopamine receptor typing is *in statu nascendi*, and quite naturally this makes it difficult to the mere observer of the scene to gain a clear overview. For the case of the dopamine receptors in the CNS this is greatly helped by a recent review (27). For an overview on peripheral dopamine receptors, mainly considering the vascular system, there also exists a recent review (21). It is apparent from the literature that important differences still exist between the various views on dopamine receptors subtypes.

Of endocrine cells equipped with dopamine receptors only three cell types have been analyzed in detail, the prolactin producing cells of the anterior pituitary lobe, the MSH producing cells of the intermediate pituitary lobe and the PTH producing cells of the parathyroid gland. Comparing the pharmacology of the prolactin and the PTH cell led to the proposition by Kebabian and Calne (25) of D_1 and D_2 dopamine receptor which transduces a stimulatory signal to an adenylate cyclase system with the PTH cell as the prototype. The D_2 receptor being a dopamine receptor which is not linked to adenylate cyclase, with the prolactin cell as the prototype. Further experience though demonstrated that dopaminergic stimulation of both the prolactin and the MSH producing cell leads to a reduction of cAMP content trough inhibition of the adenylate cyclase system (33; 9; 34). The D_1 receptor thus transduces a stimulatory, the D_2 receptor an inhibitory dopaminergic signal.

Dopamine receptors on other dopamine responsive endocrine cells such as the TSH producing cells of the rat anterior pituitary, the ACTH producing human pituitary adenoma cells or the aldosterone producing rat adrenal glomerulosa cells still are only superficially characterized (13). Evidence exists that dopamine receptors in human pituitary adenoma cells may be heterogenous (13) as evidenced by unexpected results from

radioligand studies (3).

DRUGS

In recent years more than 20 different research groups have published new dopaminomimetic compounds. Many of these compounds, including the classical ergot compounds or ergoline derivatives contain in their structure the phenylethylamine moiety of dopamine (14). This moiety is considered by many as essential for dopaminomimetic activity. But this view is too narrow as demonstrated by the existence of such recognized dopaminomimetics as piribedil, a piperazine, as EMD 23 448, an indolyl-3-butylamide (37).

Structure activity relationship (SAR) studies have been performed in various structural groups and their results have recently been admirably discussed (6). The review concludes that SAR of dopamine agonists are "exquisitely subtle and are not yet understood". Goals of synthetic work by the various research groups have been several: to increase potency and or duration of action, to create selective dopaminomimetics (if possible for one subtype of dopamine receptors), to find new patentable structures. Progress toward the three goals has certainly been achieved (see e.g. Table 1), but very few compounds have reached the stage of clinical application.

TABLE 1

Subtype-selective dopamine receptor agonists

Compound, Code name	Chemistry	Specificity	Reference
1) SKF 38393	tetrahydrobenzazepines	D_1 receptor	35
2) Ly 141865	reduced ergoline structure: pyrazoloquinoline	D_2 receptor	41
3) 3-PPP	phenylpiperidines	autoreceptor	23
4) TL-99	aminotetralines	autoreceptor	22
5) RDS-127	indeamines	autoreceptor	1

We have understandably spent much time to study the pharmacological profile of modifications on the bromocriptine molecule. As an example Figure 1 presents the subcutaneous activity of such compounds on the rat ovum implantation inhibition test in percent of the activity of bromocriptine. Only single chemical changes are considered here. Figure 1 shows that not only changes in various positions of the ergoline structure (numbered 1-14) but also changes at the "periphery", in the cyclopeptide moiety (positions numbered 1'-11') influence biological potency in an important way. Very few changes were favorable to the *in vivo* potency. Figure 2 demonstrates detailed pharmacological activities of a number of homologues in position 6 of bromocriptine (18). It is interesting to note that increasing F from methyl to ethyl changed the antagonist property of bromocriptine at the D_1 receptor to agonist activity. This new property together with an increased potency in the implantation inhibition test, was accompanied by no change in affinity to striatal ^{3}H-dopamine and ^{3}-spiroperidol binding sites, no increased emetic potency

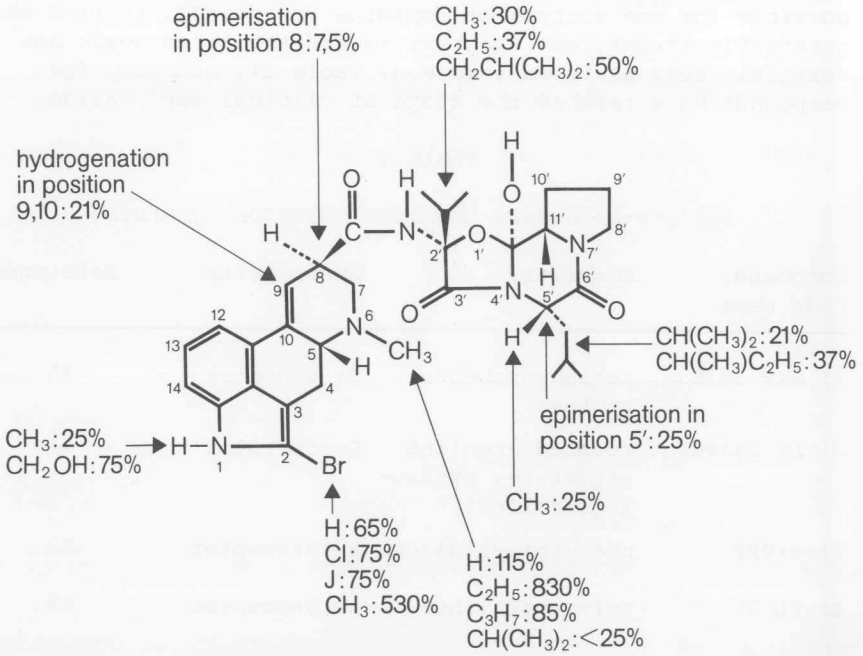
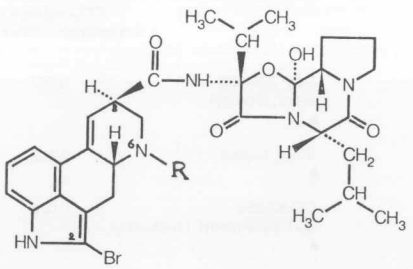


Fig. 1. Bromocriptine derivatives I: Effects of single chemical changes to the bromocriptine molecule on relative prolactin inhibitory activity in vivo.

but reduced motor effects. These qualitative changes in the profile of actions were unexpected and they are of great interest for reflections on SAR.

Similar work was done with amino-ergolines, starting from compound CH 29-717, N,N-dimethyl-N'-(6-methyl-ergoline-8α-yl) -sulfamide hydrochloride (16). In Figure 3 the structure of this compound is indicated together with the prolactin secretion inhibitory potency (as assessed *in vivo* in the classical implantation inhibition test) of CH 29-717 and some of its derivatives. In Table 2 the dopaminomimetic profiles of selected compounds of this series as assessed *in vivo* and *in vitro* are compared.

Of these CU 32-085 is of special interest (17; 19). The serum prolactin lowering potency of CU 32-085 was 40 times lower at 1 hour after s.c. administration than that of CH 29-717. At 2 hours CU 32-085 was 14 times weaker and at 8 and 24 hours 2 times less potent than CH 29-717. In the brain of treated rats DOPAC concentration was first increased after CU 32-085, indicating acceleration of DA turnover, and the



Effects	R= -H	-CH_3	-CH_2-CH_3	-CH_2-$CH(CH_3)_2$	-CH(CH_3)-CH_2-CH_3	-CH_2-CH_2-$CH(CH_3)_2$	-CH_2-CH_2-CH_2-CH_2-CH_3
Implant.inhib.rat, ED_{50} mg/kg s.c.	0.65	0.75	0.09	0.88	>3	>3	>3
Ungerstedt rat, MED, mg/kg s.c.	>10	0.1	>10	>3	>1	>1	>1
Stereotyped behav. rat, MED, mg/kg i.p.	30	0.5	30	>30	30	30	30
DA sens.aden.cyclase +agonist, -antagonist		-	+		+	(-)	(-)
Striatal affinity (binding) IC_{50} (nM) DA/SP		48/13	73/13		650/24		
Emesis, dog, ED_{50} µg/kg i.v.		7.5	5.8				
5-HT sens.aden.cyclase +agonist, -antagonist		-	+		+	(-)	(-)
A.basilaris (5-HT) +agonist, -antagonist		->+	-+				

Fig. 2. Bromocriptine derivatives II: Effect of homologuous changes at position 6 of the molecule on the profile of activities.