HIGHLIGHTS OF PHARMACOLOGY IN CENTRAL EUROPE[1]

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Condensing the pharmacological research of Czechoslovakia, Hungary, and Poland into a brief review is a difficult task. Of all the literature published, only a narrow choice, biased of course by the authors main interests, can be presented in the limited space available.

Central Nervous System

Only a minor part of performed research can be mentioned. Votava *et al.* (Prague) found that N-(3-diethylaminopropyl)homacridane hydrochloride (1); 1-(3-dimethylaminopropylidene)2,3,6,7-dibenzo suberane hydrochloride (proheptadien); 1-(3-dimethylaminopropylidene-2′-chloro-2,3,6,7-dibenzosuberane hydrochloride, (chlorproheptatrien); and 1-(3-dimethylaminopropylidene)-2′-chloro-2,3,6,7-dibenzo-4-suberene hydrochloride, (chlorproheptadien) have antidepressive effects (2). The same group also introduced new serotonin antagonists (3). Nádor and co-workers in Budapest have synthetized a number of β-aminoketones with interesting central properties (4, 5). Knoll *et al.* (Budapest) discovered in 2-piperidinomethyltetralon-1 a substance with major tranquilizing properties. These types of β-aminoketones also have anticonvulsant potencies; they potentiate the tranquilizing effect of reserpine but antagonize its influence on electroshock (6, 7, 8). Deriving from this work Pórszász, *et al.* introduced a new drug with interneuron-depressing activity, 1-piperidino-1-methyl-3-(p-tolyl)-propan-3-on (9, 10).

During the course of this work a number of psychopharmacological experimental methods were developed. Knoll & Knoll worked out a conditioned jump test with a very strong unconditioned electrical stimulus. The conditioned response remains strong without reinforcement for a long period in animals with free motility (11). This response is suppressed only by major tranquilizers (12). Kellemen, *et al.* proved that electroencephalographic changes after the application of the conditioned stimulus, acting continuously or in short intervals, maintain a desynchronization of cortical activity which is almost unextinguishible (13). In this connection, the work of Ehrlich, Frońková & Slégr (Prague) should be mentioned. In dogs they found that the adaptation of the animals to external stimuli is disturbed with chronic reserpine treatment. Many weeks after the reserpine administration was stopped, the pulse rate remained lowered (14) and phenmetrazine improved

[1] The survey of the literature pertaining to this review was concluded in June 1961.

conditioned responses to external stimuli (15, 16). With a combination of methylphenidine and reserpine, the action of reserpine predominates (17).

Metabolic studies about tranquilizer responses in the brain have been performed mainly by the group of Zelený (Pilsen, Czechoslovakia) and by Mehes and co-workers in Pécs (Hungary). Vek in Pilsen found no changes in acetylcholine synthesis in the brain after administration of chlorpromazine (18). *In vitro* oxygen consumption was lowered (19) without changes in the cytochrome system (20). However, *in vivo* no changes in oxygen consumption were found (21). According to Decsi & Mehes, chlorpromazine and other tranquilizers inhibit *in vitro* oxidative phosphorylation as well as adenosinetriphosphatase activity (22). The uncoupling effect of chlorpromazine is bound mainly to the subthalamic region, more specifically than with barbiturates (23). Both mentioned disturbances must be elicited if tranquilizing effects of the chlorpromazine type are to be present. This makes it possible to predict tranquilizing activity by *in vitro* experiments (24, 25, 26). The disturbance in oxidative phosphorylation could be prevented by sulfhydryl groups (27). The interaction of chlorpromazine and the central actions of local anesthetics were investigated by Mazur in Szczeczyn (Poland). He emphasized the importance of chlorpromazine as a central antagonist of local anesthetics in premedication (28, 29). New barbiturates were synthetized and investigated by Wilimowski *et al.* in Wroclaw (Poland) (30, 31, 32).

Catechol amine research arouses much interest, Trzebski (Warsaw) injected epinephrine, norepinephrine, and monoamine oxidase inhibitors directly into the reticular formation. Increase of electrical activity appears after a long latency and is long lasting (33). Trzebski thinks that this is a secondary action of catechol amine metabolites. Venulet (Warsaw) found a parallelism between the antagonization of the conditioned-reflex inhibiting effects of phenothiazine derivatives by serotonin and iproniazid and between the antagonism of these drugs and phenothiazine derivatives in isolated organs. On indirect evidence he suggests an antiserotonin mechanism in the phenothiazine-depressing effect of conditioned reflexes (34). A strong depletion of catechol amines in the brain was found after administration of Shigella shigae toxin, but not after staphylococcal α-toxin administration (35).

Pharmacology of the Heart

Vlk and co-workers in Pilsen found a direct parallelism between age and the amount of acetylcholine in the heart of mammals (36). Szekeres and his group in Pécs (Hungary) compared pharmacological effects on normal and hypoxic hearts. Pharmacological activity of the hypoxic heart is decreased (37). Szekeres *et al.* also compared fibrillation *in vitro* and *in vivo*. The fibrillation threshold of the isolated heart is higher (38). They also analyzed the antifibrillatory potency of drugs on atria and ventricles. Procaine and chinidine are more active on atrial, papaverine on ventricular fibrillation (39). In Krakow Oszacki *et al.* (Poland) found direct relation between EEG

changes and electrolyte disturbances in hypothermic cats (40). Comparing the properties of lanatosides A–D, Kovaříková *et al.* (Prague) found lanatoside D equal to A on heart-lung preparations. Also, their therapeutic index is the same; the most advantageous, however, is lanatoside C (41, 42).

Froněk & Ganz in Prague brought some interesting points to the use of nitroglycerine and papaverine. In dogs nitroglycerin infusion decreases the cardiac output because of reduced venous return. Blood flow through the coronary sinus is diminished, and the work of the left ventricle and the oxygen consumption are reduced. Papaverine causes a slight rise in coronary sinus blood flow. There is practically no increase in oxygen consumption in the left ventricle. The work of the left ventricle is reduced. Thus papaverine seems to be a more rational drug than nitroglycerin (44).

Pharmacology of Lipid Metabolism, Atherosclerosis, Anticoagulants

Wenke and his group (45) in Prague analyzed the discrepancy between the action of α and β adrenomimetic drugs where they can be differentiated, on carbohydrate metabolism and their action on lipolysis. This is increased in adipose tissue by all adrenomimetics and blocked by both types of adrenolytics. The authors suggest the presence of γ-receptors to explain these results (46). The same group also made the interesting observation that in the second phase of its action heparin in normal therapeutic doses leads to a paradox hyperlipemia (47). Protamin sulfate increases, under basal conditions, the level of aliesterases and lipoprotein lipase, probably by freeing endogenous heparin. This effect is not abolished by adrenolytic drugs (48, 49). Fodor & Grafnetter (Prague) found a steep decline of free fatty acids in thiopental anesthesia; ether was without effect (50). By combining subtotal thyroidectomy or methylthiouracil administration with diet (51, 52), Supniewski (Krakow), Chrusciel (Zabrz-Rokitnica, Poland), and co-workers developed marked atherosclerosis in pigeon. On this model a simple phosphorus compound (53) and methionine (54, 55) had favorable effects. Samochowiec (56) recently claimed antiatherogenic effect for extracts of Scynara Scolymus; Supniewski and co-workers for 2-methyl-2-butene-carboxylic acid (57).

Trčka (Prague) has shown that the substitution of one coumarin ring by chromone leads to a significant increase and prologation of anticoagulant activity (58). Kovalčík *et al.* (Bratislava, Czechoslovakia) have investigated analgetic effects of anticoagulant drugs of the phenylindandione type. Whereas these derivatives are analgetic (59, 60), they could not confirm analgetic properties of 4-hydroxycoumarin (61).

Antibiotics

Using the fluorescence technique, Málek & Kolc (Prague) have shown that chlortetracycline is taken up by necrotic pancreas and remains there for a long period (62, 63). The drug also accumulates in ischaemic tissue of the kidney, the heart, and the liver (64). Sobek and co-workers (Prague)

considerably reduced the ototoxicity of neomycin by simultaneous administration of vitamin D_2 in guinea pigs (65). The results were confirmed microscopically on the Corti organ. Attention was paid to the pharmacology of racemic and optically active forms of antibiotics. Trčka & Horáková showed that D-chloramphenicol has central depressing activity (66), whereas the L-form possesses convulsive properties (67). Rašková *et al.* showed in a controlled clinical trial that racemic cycloserine has a significantly higher ratio of severe side effects in the central nervous system than the D-form (68).

Radiopharmacology

Changes in the effects of drugs in irradiated animals interest Danysz (Bialysztok, Poland) and Grossmann (Hradec Králové, Czechoslovakia). Danysz found an increased sensitivity to epinephrine, whereas the effects of monoamine oxidase inhibitors were weakened (69, 70). The animal species and kind of anaesthesia seem to be important, since Grossmann saw in rats with epinephrine and norepinephrine a weakening of hypertensive effect (71). Danysz also found a weakening of the acetylcholine, pilocarpine, and neostigmine effects on isolated organs of irradiated animals (69, 70). Meperidine (pethidine) metabolism is altered (71, 72); the action of some barbiturates is prolonged (thiopental); others are shortened (phenobarbital). The potency of pentylenetetragol (Metrazel) is increased (73).

Inflammation, Nonspecific Resistance, Toxins

The mechanism of inflammation is studied by Jancsó in Szeged (Hungary). On his evidence one part of inflammatory events depends on intact sensory innervation, whereas another part is accomplished by the freeing of various substances (74). Repeated injection of capsaicin produces tolerance to its pain-producing properties and also to that of other irritants (75). The antiinflammatory potency of many drugs has been studied by Lenfeld *et al.* in Olomouc (Czechoslovakia). Emetine and new phenylbutazone derivatives were very effective (76, 77). Hladovec *et al.* found antiinflammatory properties in a potato protease inhibitor (78). Nonspecific resistance to bacterial toxin, shock, and infection can be induced by repeated phenol injections. The increase in resistance is transmissible by blood and by milk from mother to young; it is transient (79, 80). All work concerning bacterial toxin has been (81) and will be (82) reviewed elswhere.

Those wanting to broaden their knowledge about pharmacology in central Europe will find all essential information in *Acta Physiologica Polonica* (English summaries) (83), *Acta Physiologica Academiae Scientarium Hungaricae* (in English and German) (84), *Physiologia Bohemoslovenica* (in English) (85), and *Československá fysiologie* (Proceedings of the Czechoslovak Pharmacological Society meetings, in Czech (86).

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