molecular integrity of this filtration membrane and be responsible for the increased permeability of the glomerular capillary to protein. The quantitative differences in MUPpg excretion in different groups is difficult to explain but may reflect increased loss of glycoprotein components in the urine in nephrotic rats. It is also possible that the increased quantities of MUPpg result from errors in the quantitation of MUPpg excretion by the techniques used since MUPpg may be lost in the isolation procedure described.

Since the nephrosis in rats produced aminonucleoside of puromycin bears a striking clinical, morphologic and immunohistological resemblance to lipoid nephrosis in the human the mechanism of production of disease by this drug may have striking pathogenic and therapeutic application[19].

Résumé. La néphrose produite expérimentalement chez le rat par l'amino-nucléoside, qui est analogue à la néphrose lipoïdique chez l'homme, est associée à des changements de la composition des glucides d'une glucoprotéïne non collagène extraite des urines de rats ayant de la protéinurie. La composition des acides aminés n'a pas changé. Il se peut que cette glucoprotéine soit le résultat d'altérations dans la membrane basale glomérulaire, altérations qui amènent la protéinurie et peuvent être importantes dans la pathogénèse de la néphrose lipoïdique chez l'homme.

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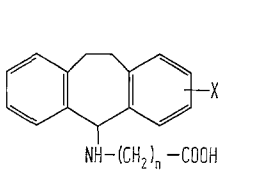
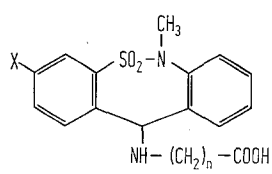
7-Aminoheptanoic Acid Derivatives as Potential Neuropharmacological Agents. I

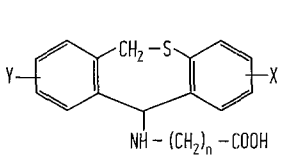
Short chain amino-acids, such as glycine or 4-aminobutyric acid[1,2], are generally appreciated as mediators in nervous central inhibitory systems. Long chain amino-acids such as 6-aminohexanoic[3,4] and 8-amino-octanoic acids[5–10] are evaluated as possible stimulant substances acting upon the central nervous system; consequently it seemed important to study systematically a large number of aliphatic ω-amino-acids derivatives. As part of this program, we have synthetized a large number of linear ω-aminoalcanoic acids N-substituted with a tricyclic nucleus, previously known for its affinity towards central nervous system structures. This choice led us to synthetize four important series of compounds having the following 4 general formulas:



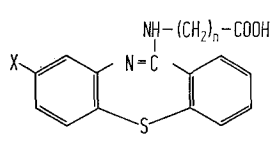
I



II



III



IV

Pharmacological screening methods. a) mice motor activity during 2 h using an actophotometer APELAB[11]; b) group toxicity in CD mice[12]; c) hyperthermia in LE rats and rabbits; d) anorectic potency in the SD rat[13]; e) antagonistic effect against reserpine or barbiturate depression or f) against reserpine-ethanol induced sleep in mice[14]; g) tail-clip test for analgesia; h) hot plate technique in NMRI mice[15]; i) antitussive activity using a citric acid spray in the guinea-pig[16]; j) cardio-vascular effects were determined in the nembutal anesthetized dog: blood pressure, heart rate, cardiac output, respiratory frequency and interactions with vaso-active mediators after i.v. injections of compounds; k) EEG studies were realized in chronically implanted rabbits and rats (CD); l) in vitro tests including ileum, vas deferens, seminal vesicle and uterus.

Results. In the series I and with n increasing, there appeared suddenly with $n \geqslant 6$ a motor stimulant effect after i.p. or oral administrations to mice. This activity slowly decreased for $n \geqslant 10$.

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The most active compound of the series was N (dibenzo (a, d) cycloheptadien 5 yl)-7 aminoheptanoic acid hydrochloride (S 1694). After 25 mg/kg p.o., a 174% increase appeared in motor activity above controls in method a). S 1694 at 5 mg/kg i.p. in the rat induced a cortical activation linked to an hippocampal hypersynchronizating effect of long duration. Moreover, S 1694 could antagonize the depressive state and hypothermia in reserpinized mice: motor stimulation appeared again in this test after 5 mg/kg i.p. Barbiturate sleep was equally shortened after the i.v. administration of the same dose.

S 1694 did not induce the so-called group toxicity phenomenon in mice (LD 50 = 405 mg/kg p.o. (496—331) in aggregated mice; LD 50 = 520 mg/kg p.o. (593—463) in isolated mice). Hyperthermia did not appear in the rat up to 40 mg/kg s.c. A slight thermal reaction ($\Delta t = +1.05$°C) appeared in the rabbit after 30 mg/kg i.v. There was no decrease of food intake in the rat up to 40 mg/kg p.o., and no analgesia up to 50 mg/kg p.o. in mice. After the i.v. infusion of 10 mg/kg, the hemodynamic parameters were not modified in the dog (method j). There were no changes in pressive responses to epinephrine or norepinephrine. Thus it could be concluded from these results that compounds of this series I could act on the central nervous system as new stimulants.

As in the series I, compounds of the series II were first tested as motor stimulants in rodents, but an analgesic activity appeared in methods g) and b). The activity ratio of the most active compound of this series (sodium N(8-chlorodibenzo (c, f)[1,2] thiazepin-5-yl)-7 aminoheptanoate (S 1574) compared to D-propoxyphene in the tail clip test (method g) after s.c. administration was 0.77; on the hot plate test, the ratio was 1.3, orally (method h). Compared to codeine phosphate in the antitussive assay i), the relative potency of the compound was 5.2 (s.c.). The analgesic activity seemed to be centrally mediated, mainly because of behavioural modifications appearing with higher dosages and also EEG changes (cortical arousal followed by a slow electrocortical-activity in the rat). The position of the X substituant seemed to be critical in the series II, since any change in other position near entirely suppressed the pharmacological activities.

In the series III, with X = Cl, Y = H and n = 6, a pharmacological activity appeared, mainly of a motor stimulant nature in mice and rats. The most important compound was N (3-chlorodibenzo (b, e) thiepin-11 yl) 7 aminoheptanoic acid hydrochloride (S 2017). The motor stimulant effect of this compound studied in method a) was pratically equal to the stimulant effect of S 1694. Compound S 2017 had no analgesic potency in methods g) and h) for doses up to 50 mg/kg p.o.

Compounds of series IV, mainly with X = CF_3 or Cl, showed a depressive potency on spontaneous motor reactions in mice and rats. Moreover it appeared an EEG arousal in cortical derivations in the rat, following the oral administration of 25 mg/kg of the most representative compound of this series: N-(8-trifluoromethyldibenzo (b, e)[1-4] thiazepin 11 yl)-7 aminoheptanoic acid (S 1976). This first phase of activity was followed by a depressive pattern, with slow and high voltage cortical waves. There appeared at this moment a slight decrease in body temperature with method c) in rats. A myorelaxing effect was present with higher doses (100 mg/kg p.o.) but no hypnotic effect was noted in rats. The compound, according to method f), could antagonize the reserpine-ethanol induced sleep in mice (60% decrease in sleeping time was observed after the administration of 5 mg/kg i.p.). In the anesthetized dog, pressive responses to epinephrine or norepinephrine were reduced after 5 mg/kg i.v. Compounds of the series IV were considered as new sedatives agents. They could slowly depress the exploratory behaviour in rats and mice, and also the muscular tone and reflexes. The compounds could not directly induce sleep or catatonia on the one hand, but they could on the other hand antagonize the reserpine-ethanol induced sleep. Finally the compounds could act on CNS in a biphasic manner: a short stimulating phase followed by a depressive one.

The most active compounds of each series were tested on isolated organs in vitro (method l). Compounds of all series had no anticholinergic potency. Compounds of the series IV had a slight adrenolytic potency. A slight antiserotonin activity was found with the most potent compounds of the four series.

As a rule, in the 4 series, the terminal COOH could be replaced by a COOR group or a CH_2OH group. Their pharmacological effects were qualitatively and quantitatively preserved. The substitution of the COOH group by a methyl group totally inhibited the activities. As a rule N methylation suppressed also the activities.

Finally the ramification of the amino acid chain was studied with $n = 6$

$$R\text{–}NH\text{–}\overset{7}{C}H_2\text{–}\overset{6}{C}H_2\text{–}\overset{5}{C}H_2\text{–}\overset{4}{C}H_2\text{–}\overset{3}{C}H_2\text{–}\overset{2}{C}H_2\text{–}COOH$$

In the series I the substitution by 1 or 2 methyl groups in position 4 and 5 suppressed the motor stimulating property. The substitution by one methyl group in positions 2, 3, 6 or 7 maintained this activity. In the series II, whatever the position of the methyl substituant, the analgesic activity was always maintained.

Discussion. The amino acid derivatives described have neuropharmacological properties of a wide scale; furthermore their activities on the autonomic nervous system seem to be weak. The derivatives bearing a polar acidic function pass through gastro-intestinal and blood-brain barriers. The main feature of all the structures is the presence of an aliphatic amino acid chain, which is strictly necessary in most of the series for obtaining the activities. Various tricyclic nuclei seem to differentiate neuropharmacological properties of the compounds to a certain extent.

Some questions may arise from these neuropharmacological findings: considering different kinds of pharmacological potencies, is there a real pharmacological unity in these ω-aminoacid derivative? Are compounds interferring directly of indirectly with known neurotransmitter systems, or are they acting on inhibitory amino acid systems recognized by many authors? In this case, compounds would appear as original neuropharmacological agents. Studies are now in progress in order to elucidate these problems. More chemical and neuropharmacological data will be published later.

Résumé. De nombreux dérivés d'ω-amino-acides aliphatiques ont été synthétisés. Lorsque le N substituant est un noyau tricyclique et la chaine aliphatique contient au moins 6 chainons, on obtient des composés neuropharmacologiques. Le maximum d'activité est atteint pour les dérivés d'acide amino-7-heptanoïque.

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