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Concluding Remarks

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THESE remarks aim to put into focus the highlights of the second session of the symposium on non-benzodiazepine hypnotics and anxiolytics. The short but very dense meeting has brought together a number of scientists who have provided the forefront results of this new, major direction in research. In fact, sleep disorders and anxiety represent serious medical problems. As mentioned by Dr. Lader, a substantial part of the western population uses occasionally (10–20%) or permanently (3–8%) hypnotic and antianxiety drugs. For 20 years these drugs have been represented almost exclusively by benzodiazepines (BDZs), due to their efficacy and relatively low general toxicity. However, there are several drawbacks which are inherent to this class of agents: thus, BDZ hypnotics do induce alterations of sleep architecture (decrease in stages 3 and 4) and, accordingly, of sleep quality; carry-over effects of long half-life BDZs with impairment of day performances are well known; cognitive and memory disturbances frequently occur; rebound insomnia, day time anxiety, irritability and psychotic reactions are caused, with variable incidence, by short acting compounds. BDZ anxiolytics usually exhibit sedation, muscle relaxation, memory and cognitive impairment. Both anxiolytic and hypnotic BDZs induce tolerance, though to a different extent, physical dependence can occur.

On this background it appears that the new classes of compounds discussed at this meeting certainly represent a major progress over existing BDZs. They are the result of extensive neuropharmacological and clinical research aimed at identifying novel mechanisms of action and defining their impact on therapeutics.

The first problem which was raised in this Symposium refers to nomenclature. As discussed by Dr. Langer, compounds structurally different from BDZs such as imidazopyridines (zolpidem, alpidem) or cyclopyrrolones (zopiclone) and many others bind to sites previously designated as BDZ recognition sites. On this basis, this latter designation has to be changed and the proposal of Langer and co-workers to replace BDZ_1, BDZ_2 and peripheral BDZ sites by ω_1, ω_2 and ω_3, respectively, has a strong rationale. This proposal is not only based on the variety of chemical classes which bind to the same site on which BDZs act, but also on the identification of ligands which exhibit selectivity for (in contrast to BDZs which do not differentiate between) one or the other ω site. This selectivity has probably a major bearing on the way by which compounds such as the imidazopyridine hypnotic zolpidem affect the supramolecular GABA receptor-ω site-Cl^- channel complex. Indeed, zolpidem exhibits a great GABA shift and a minimal Cl^- effect (Langer, this Symposium) and a peculiar TBPS binding (Lloyd, this Symposium). It is tempting to relate these features to the clinical spectrum of zolpidem: no change or increase in stage 3 and particularly 4 (Gaillard, this Symposium) and absence of alterations of CAP (Terzano, this Symposium), properties which probably explain the optimal quality of sleep; the virtual absence of changes in paradoxical sleep (Gaillard, this Symposium); the absence of effects on the day after (although this is also related to the optimal kinetic and metabolic features of zolpidem; [3]), the absence of rebound insomnia as well as of mood and cognitive alterations (Wheatley, this Symposium) which are seen for instance with triazolam. Similarly, the absence of muscle relaxation is probably linked to the fact that zolpidem does not act on ω_2 sites present in the spinal cord. Finally, the low potential for tolerance and, apparently, dependence [3] do further distinguish the pharmacological and clinical spectrum of zolpidem from that of BDZs.

Zopiclone is a member of another chemical class with affinity for ω sites. Its selectivity for ω_1 sites is less pronounced than that of zolpidem as zopiclone also binds significantly to ω_2 sites (Langer, this Symposium). From the (unfortunately short) report of Dr. Brun in this Symposium and from literature data [1] it appears that zopiclone displays a clinical spectrum which is intermediate between those of zolpidem and classical BDZs such as flunitrazepam and triazolam, but which is closer to that of the latter compounds: this refers to changes in stages 3 and 4 and in paradoxical sleep, to the occurrence of rebound insomnia and anxiety, to the effect on psychomotor performances the morning after and on memory. The pharmacological and clinical spectrum of zopiclone close to that of BDZs, as compared to the binding and clinical profile of zolpidem, support the preponderant role of ω_1 sites for selective therapeutic features.

Two other compounds with anxiolytic properties have been discussed at this meeting: alpidem and buspirone.

Alpidem belongs to the chemical class of imidazopyridines. Similar to zolpidem, alpidem binds to ω_1, and is practically inactive on ω_2 sites. As mentioned for zolpidem, this selectivity parallels a peculiar spectrum of alpidem on the supramolecular complex in as much as the compound exhibits a greater GABA shift as compared to BDZs and the virtual absence of Cl^- effect (Langer, this Symposium). Again, these biochemical features are associated with a very selective clinical profile: anxiolytic action comparable to that of BDZs in the absence of effect on memory (Lader, this Symposium) and muscle tone ([3]; this latter effect being explained by the absence of binding at ω_2 sites). Moreover, therapeutic doses of alpidem not only do not deteriorate cognitive functions, but also induce improvement in some psychometric tests (Lader, this Symposium). Alpidem

displays a very minor effect on vigilance: even at doses exceeding 5 or 10 times the therapeutic ones no sleep occurs (Musch, personal communication). Tolerance to alpidem does not seem to occur and dependence was not observed at withdrawal from one year treatment (Musch, this Symposium).

It remains to be explained why zolpidem exhibits a potent sleeping inducing action whereas alpidem is an anxiolytic devoid of effect on vigilance, while both compounds act at the same ω_1 site. Also, both compounds do not bind at known receptors or other sites, with one exception however: alpidem, at variance with zolpidem, binds to ω_3 sites (Langer, this Symposium). This may play a role as for the difference in the spectrum of the two imidazopyridine compounds, though the function of ω_3 sites has not been identified as yet.

Buspirone, a decanedione compound, also opens a new way in the therapy of anxiety. It is not only a non-BDZ, but also possesses a different mechanism of action, acting probably via $5HT_{1A}$ receptors [2]. The blockade by buspirone of D_2 receptors is likely not connected with the anxiolytic action but with possible extrapyramidal side effects. The action of buspirone in behavioural tests is not blocked by BDZ antagonists and, in the generalization test, animals do discriminate buspirone from BDZs. This supports the different mode of action and may explain the subjective experience of patients to buspirone which is different from that to BDZs. Also, the preference of patients for buspirone seems to be less pronounced than that for BDZs. This may be connected to inherent features of buspirone and/or to the apparent long onset of its anxiolytic action (1 to 2 weeks). Buspirone is apparently devoid of muscle relaxation, tolerance and dependence and shows a low potential for sedation. The data presented by Dr. Sheehan in this meeting indicate, however, that buspirone is devoid of action in panic disorders, similarly to BDZs.

In conclusion, this Symposium has focused on compounds which are chemically different from BDZs and display new mechanisms of hypnotic and anxiolytic action such as selectivity for ω sites (imidazopyridines: zolpidem and alpidem; cyclopyrrolones; zopiclone) as well as for $5HT_{1A}$ (buspirone) or $5HT_2$ receptors (ritanserin): this opens new paths in the elucidation of the relation between modes of action and clinical features. However, several problems remain to be solved such as the differential mechanism of hypnotic vs. anxiolytic agents which apparently act at the same site (ω_1 for imidazopyridines); or the common anxiolytic mechanism which has to be triggered by compounds as different as buspirone and BDZs. This will certainly be a matter for a new Symposium some years from now.

I would like to conclude by emphasizing the enormous role which the finding and definition of new drugs by pharmacological and clinical research play in the advancement of basic knowledge and therapeutics: thus the discovery of agents such as imidazopyridines, cyclopyrrolones and decanediones will result both in a better understanding of the role of receptors and neurotransmitters in brain mechanisms such as sleep, anxiety, cognitive functions and in the safer and more effective treatments which will be available in the near future.

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