review articles

Halopemide, a new psychotropic agent

Cerebral distribution and receptor interactions

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Clinical profile

Halopemide (R 34301, Fig. 1) is a derivative of butyrophenone-type neuroleptics, developed by one of us[1] and designed as an anti-emetic drug, which, after pharmacological and clinical testing, turned out to possess unique psychotropic effects.

Preliminary clinical results indicate that halopemide may be a 'psychic energizer' of use in the treatment of withdrawn, inactive patients.[2] Wauters and Rombaut observed a significant improvement in eight out of ten female schizophrenic in-patients after switching from a usually moderately effective long-term neuroleptic treatment to a daily oral dose of 22.5-60 mg halopemide in an open pilot trial. The effect on autism, hallucinations and delusions was highly significant, but agitation was not affected.[3] Deberdt showed in a double-blind trial that halopemide (7.5 mg orally, twice daily) was superior to placebo in ten young male oligophrenic patients with pronounced autistic behaviour after abrupt withdrawal of all previous neuroleptic medication. The five halopemide-treated patients had become more alert, communicative and seemed to be activated. One patient spoke for the first time in an adequate manner after receiving halopemide.[4] In an open pilot follow-up halopemide again was found to be most effective in patients with severe autistiform behaviour, when agitation was not a primary symptom. Veltkamp reported spectacular improvement of a 16 year old infantile autistic girl treated with 7.5 mg twice daily.[5]

Depoorter *et al.* treated seventy out-patients with a wide variety of diagnoses and poor contact and energy as selection criteria, with oral halopemide (usually 10 mg twice daily) in addition to previous treatment in a multicenter open trial.[6] Forty-six patients clearly benefited from the treatment with halopemide. Most of them were young schizophrenic patients with clear autistic symptomatology (20 of 34). Improvement was also noted in neurosis (11 of 16), especially in hysterical and neurasthenic patients. It seemed to energize some depressive patients (10 of 13). Halopemide facilitated contact and promoted activity. Agitation, anxiety and suicidal tendencies seemed to be contra-indications.

In order to validate these observations, a double-blind cross-over study was initiated.[2] Fourteen responders – again with various diagnoses – received halopemide during the first or second phase of the study in comparison to placebo during the other phase. The daily dose corresponded with the optimum daily dose as determined in the open trial. Nine patients clearly deteriorated during the placebo period. De Rooy (Psychomedical Health Centre 'Welterhof', John F. Kennedylaan 301, Heerlen, The Netherlands) and Van Wijngaarden (personal communication) observed energizing, activating effects in eighteen patients with a neurasthenic-hypochondriacal depressive neurotic syndrome treated with a daily dose of 20-40 mg halopemide, of which all showed improvement. Nolen and Jadnanansingh switched from non or inadequately effective neuroleptic treatment to halopemide in eleven chronic or residual schizophrenic patients with autistic symptoms. They observed a disinhibitive and activating effect in seven patients, but no antipsychotic effect.[7]

Antipsychotic agents exert various side effects.[8-11]

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Abstract

Halopemide is a new psychotropic agent, a structural analogue of the neuroleptics of the butyrophenone type but with different pharmacological and clinical properties. Preliminary clinical findings indicate that halopemide lacks the ability to induce parkinsonism and may be an effective drug in the treatment of psychosis characterized by autism, emotional withdrawal or apathy. Its pharmacological effects at a molecular level in comparison to structurally related neuroleptics and putative metabolites are reviewed.

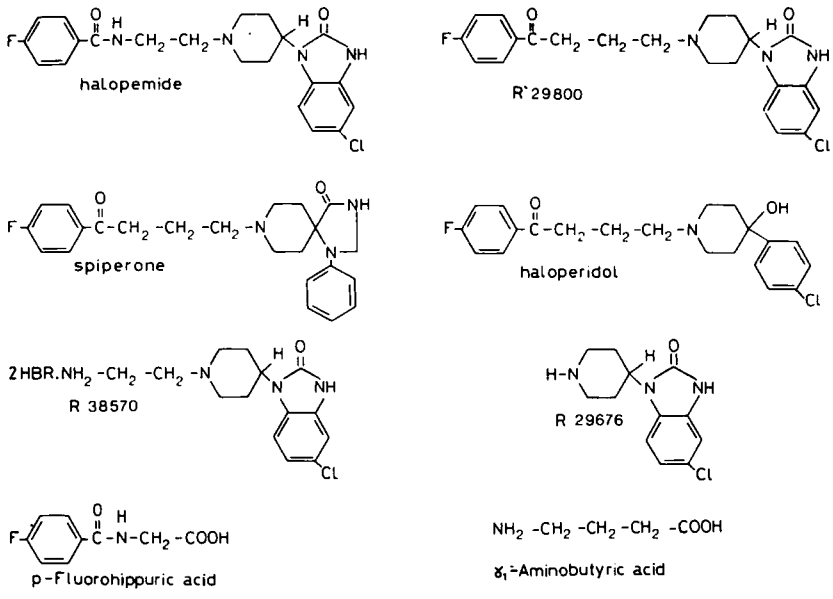

FIGURE I
Structural formulas of halopemide, its putative metabolites, related neuroleptics and GABA

Many of these are extensions of their pharmacological actions. The most dramatic and, pharmacologically, the most important group of side effects shown by all 'classical' neuroleptics are the extrapyramidal reactions.[12-16] This family of side effects can be classified into three arbitrary categories:[8]

- a syndrome akin to Parkinson's disease (*e.g.* akinesia, tremor at rest, rigidity and the rabbit syndrome);
- akathisia (uncontrollable motor restlessness);
- dyskinesias (involuntary bizarre movements), which can be subdivided into acute dystonic reactions (*e.g.* torticollis, oculogyric crisis, opisthotonus) and tardive dyskinesia: late-onset dyskinesias with potential irreversibility.

In none of the clinical studies did halopemide produce parkinsonian side effects. Wauters and Rombaut reported hyper- and dyskinesias,[3] which might be due to withdrawal from previous neuroleptic treatment (tardive dyskinesia). This was also observed by Nolen and Jadnanansingh,[7] who in addition reported halopemide to cause akathisia.

Other side effects which have been reported include loss of appetite,[3] elevated sedimentation rate and vomiting.[7] Halopemide increases serum prolactin both in patients[7] and in healthy volunteers.[17]

It may be concluded, that the clinical profile of halopemide differs from the properties of classical butyrophenone neuroleptics. The drug seems not to induce similar therapeutic effects and lacks parkinsonian side effects. In the present article we review and reinterprete the work which has been done, largely by ourselves,[18 19] on its molecular pharmacological properties.

The aim of our studies was to elucidate the mechanism of action and to find an explanation for the absence of parkinsonian side effects. Therefore, we have studied the distribution profile of halopemide in the rat brain *in vivo*. As serotonergic transmission may be impaired in early infantile autism, we have investigated its effects on serotonin uptake and release. Possible interactions with GABA-ergic mechanisms have been studied, as these may be related to its lack of extrapyramidal side effects.

Regional localization in the rat brain

It has been shown that the administration of neuroleptic drugs to the intact animal results in a selective accumulation within those brain areas which are supposed to be enriched with dopamine receptors.[20-24] The regional distribution of neuroleptic drugs in the brain corresponds to the number of neuroleptic binding sites, which have been measured *in vitro*.[25-27] Therefore, the regional cerebral distribution of psychotropic drugs may be used to demonstrate the presence of specific binding sites *in vivo*, provided that non-specific binding is relatively constant. The latter seems to be the case with neuroleptics of the butyrophenone-type and structurally related drugs.

The concentration of halopemide in different parts of the rat brain has been compared with those of R 29800, its butyrophenone analogue, and of spiperone, both typical butyrophenone neuroleptics (see Fig. 1), after systemic administration of tritium-labelled drugs.[22] The total brain concentration of halopemide is about ten times less (Table 1). In the hypophysis, however, relatively high and mutually comparable levels are reached. Halopemide is, unlike related neuroleptics, not preferentially taken up by dopamine-rich brain areas, such as the nucleus caudatus, the tuberculum olfactorium or the nucleus accumbens. The highest level is found in the caudal part of the septal area and the thalamus (striae

medullares). Neither the percentage of the dose which enters the brain, nor the distribution profile is altered upon a 160-fold increase of the dose[22] or upon chronic treatment,[28] which hardly indicates a specific (*i.e.* saturable) interaction.

Subcellular distribution experiments show that in the caudate nucleus halopemide is far less particle-bound (*i.e.* receptor-bound) than are neuroleptic agents.[22] The low penetration into the brain is probably not due to intensive binding to plasma proteins. Such an explanation is not in agreement with the high levels reached in the pituitary gland and does not explain its different cerebral and subcellular distribution (Fig. 2).

In order to elucidate whether the distribution profile changed in time, the regional distribution has also been studied up to eight hours after the injection of a single dose.[28] The distribution profile does not change significantly up to four hours. Still, halopemide is extensively metabolized and eliminated rather fast from rat plasma ($t^1/_{2\beta}$ = 2.5 h). After subcutaneous administration the maximal plasma concentration is reached within thirty minutes, whereas the maximal brain concentration is reached in one to two hours. Thereafter, the brain concentration declines slowly. As the ratios of the unaltered drug levels in brain and plasma assayed by the isotope dilution method is steadily increasing, it may be concluded that penetration into the brain is a rather slow process.

TABLE I

*Distribution of halopemide, R 29800 and spiperone in the rat brain and the concentration of unchanged compound in brain, blood and plasma**

	Halopemide	R 29800	Spiperone
Plasma	4.80	1.87	1.09
Hypophysis	27.50	25.12	30.53
Myelencephalon	0.36	2.81	2.36
Pons	0.33	3.17	2.49
Hypothalamus	0.40	3.56	2.51
Thalamus (striae medullares)	0.57	3.14	2.47
Caudate nucleus	0.36	8.07	6.61
Nucleus accumbens	0.30	7.15	6.66
Septal area, caudal	0.70	3.43	2.54
Tuberculum olfactorium	0.31	4.93	4.77
Cortex	0.34	3.21	2.56
Blood †	5.69	5.37	4.36
Plasma †	7.81	7.23	3.90
Percentage of the dose in the brain	0.013	0.113	0.106

*Concentrations (expressed as pg/mg wet tissue) have been measured one hour after subcutaneous administration of 0.02 mg/kg radiolabelled drug, which is the ED50 of R 29800 and spiperone in protecting rats from the apomorphine-induced stereotyped behaviour. For each drug about 72-75% of the radioactivity was due to unaltered compound.[22]
†Drug plus metabolite expressed as pg unchanged drug per µl.

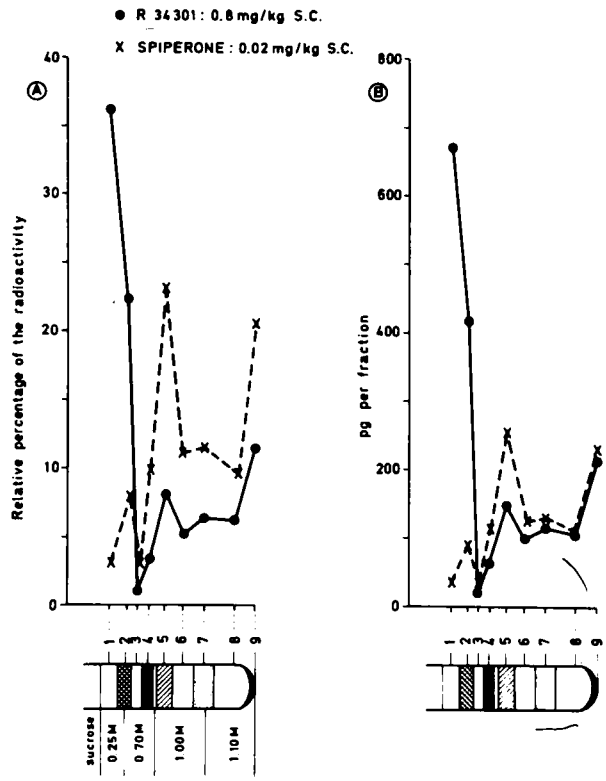

FIGURE 2
Subcellular distribution of labelled material [expressed as relative percentages per fraction (A) or as pg per fraction (B)], in the nucleus caudatus of the Wistar rat one hour after administration of halopemide (0.8 mg/kg subcutaneously) or spiperone (0.02 mg/kg subcutaneously). The concentration of halopemide in the nucleus caudatus is about twice that of spiperone (if expressed as pg/mg total wet tissue)[22]

Halopemide is preferentially accumulated by the pituitary gland, which is not protected by the blood-brain barrier.[22 28] In contrast to the brain and the blood plasma, metabolites are never detected in this gland.

Pharmacodynamic interactions

The pharmacologic effects elicited by halopemide are at various points dissimilar to those of classical neuroleptic agents.[29-34] Halopemide is a potent inhibitor of apomorphine-induced vomiting in dogs.[35] It is relatively slow and long acting and very well absorbed when given orally (ED50 = 0.1 mg/kg orally and 0.056 mg/kg subcutaneously; t_{max} = 4 h; duration of action = 12 h). However, its ability to inhibit learned conditioned shock-avoidance behaviour (jumping box test) is strikingly low.[35] The dissociation factor between the two effects, which is believed to reflect the incidence of parkinsonian side

effects,[33 34] is therefore very large (147) as compared with ratios obtained with 'neuroleptics', such as haloperidol (3), pimozide (12), metoclopramide (8) or sulpiride (91).[35]

Furthermore, the activity of halopemide in various behavioural test models is low. Catalepsy, palpebral ptosis, antagonism of amphetamine- and apomorphine-induced stereotypies, inhibition of intracranial self-stimulation and a decrease of food consumption are observed in rats at oral doses ranging from 2.5 to 20 mg/kg.[35] Typical neuroleptics are far more active in these tests.[29 32-34]

In addition, halopemide is devoid of anti-tryptamine and anti-noradrenaline effects (ED_{50} > 160 mg/kg, orally).[35] Halopemide (10 mg/kg subcutaneously) increases homovanillic acid (HVA) levels in whole rat brain, which is classically believed to reflect increased dopamine turnover due to dopamine-receptor blockade,[27 36] but seems to be less potent than haloperidol and even metoclopramide.[37]

Nevertheless, halopemide seems to affect the CNS. Wauquier and Van den Broeck have compared the effects of single (equi-anti-emetic) doses of halopemide, haloperidol and pimozide on sleep–wake patterns in dogs and have found halopemide (0.63 mg/kg subcutaneously) to cause effects opposite to neuroleptics.[38] Halopemide inhibits REM sleep for example, an effect also elicited by tricyclic antidepressants, MAO-inhibitors and psychostimulants. Daniels *et al.* report halopemide (lowest effective dose: 0.04 mg/kg subcutaneously, twice daily) and sulpiride (2.5 mg/kg) to have unique, dose-dependent effects on the stimulation of maternal behaviour in male rats, an animal model for social behaviour.[39] Furthermore, high doses of halopemide (10 mg/kg orally) have been reported to elicit acute dyskinesias, a neuroleptic-induced acute extrapyramidal syndrome, in squirrel monkeys.[40]

INTERACTION WITH DOPAMINERGIC TRANSMISSION

From its pharmacological and clinical profile it may be concluded, that halopemide elicits antidopaminergic effects. Similar to neuroleptics, halopemide antagonizes the effects of apomorphine at the level of the chemoreceptor trigger zone (CTZ),[35] an antidopaminergic effect which results in an anti-emetic action.[11] Several findings suggest that halopemide binds to pituitary dopamine receptors. Halopemide has been observed to induce an increase in prolactin levels.[7 17] Pituitary prolactin secretion is under inhibitory dopaminergic control.[27 41] Halopemide blocks apomorphine-induced growth hormone response *in vivo*[17] and stimulates apomorphine-suppressed prolactin secretion from cultured rat pituitary cells *in vitro*.[42] In the latter experiment, the potency of various dopamine antagonists, including halopemide, closely parallelled their rank order in displacing ^{3}H-haloperidol binding in rat striatum *in vitro*.[42]

It has been shown that the hypophysis contains dopamine D_2 binding sites, which are very similar to striatal dopamine receptors.[27 43] We have demonstrated relative accumulation of halopemide to occur within the hypophysis.[22 28] The concentration of halopemide in the pituitary gland is about a hundred times that of the brain and about ten times that of plasma. We have measured the concentrations at different time intervals after subcutaneous administration of halopemide.[28] When the plasma level decreases gradually, the tissue plasma ratio increases in the course of time from about 4 (30 min) to 22 (8 h after administration). In addition, in contrast to the plasma and the brain, metabolites are never detected in the gland, which would be expected when the relatively high concentrations are due to non-specific mechanisms. These facts indicate a selective uptake and retention of halopemide in the pituitary gland.

However, both the CTZ and the hypophysis are not protected by the blood-brain barrier and halopemide lacks several CNS antidopaminergic effects (*vide supra*). Halopemide has a low activity in various behavioural test models,[35] which correlate with antidopaminergic activity.[44] Among the extrapyramidal side effects of neuroleptics only parkinsonism seems to be intricately connected with a direct inhibition of dopaminergic transmission,[15] while tardive dyskinesia perhaps corresponds to an increased sensitivity of dopamine receptors due to chronic blockade.[13 14 16 43] Clinically, halopemide seems to have a low potential to induce parkinsonism and it hardly suppresses dyskinesias due to withdrawal from previous neuroleptic treatment.[3 7] Nevertheless halopemide displaces ^{3}H-haloperidol (IC_{50} = 10 n*M*) and ^{3}H-spiperone (IC_{50} = 130 n*M*) from rat striatal membranes *in vitro*.[27 45]

From what precedes it might be concluded, that halopemide lacks the ability to interfere with part of the CNS dopaminergic system due to a poor penetration through the blood-brain barrier. This seems to be confirmed by our own experiments in which it was shown that the concentration in the rat brain is rather low in comparison to those of R 29800 and spiperone.[22 28] However, halopemide is, unlike related neuroleptics, not preferentially taken up by dopamine-rich areas. As shown in Figure 2, the subcellular distribution of halopemide in the caudate markedly differs from that of spiperone.[22] Only a minor portion is, in contrast to neuroleptics, associated with (receptor-containing) particulate matter. This indicates that apart from poor penetration another factor prevents halopemide to interact with neuroleptic receptors. It may be postulated that a metabolite prevents ^{3}H-halopemide binding to neuroleptic sites *in vivo*. The exact mechanism remains to be elucidated.

INTERACTION WITH SEROTONIC TRANSMISSION

As has been indicated above, halopemide may be of benefit in the treatment of (early infantile)

autism.[4,5] It has been suggested that alterations in serotonin (5-HT) metabolism may occur in association with infantile autism.[46-49] Approximately 30% of early infantile autistic and 50% of mentally retarded children other than those with Down's syndrome (in whom the concentrations are abnormally low) show hyperserotonaemia.[46-48] In autistic children these increased levels are due to an increased serotonin content of thrombocytes,[46,47] the thrombocyte number being normal.[50] There are some indications that a low turnover rate of serotonin and/or a high turnover rate of dopamine in brains of autistic children correlate with the severity of (specific) symptoms in at least subgroups of patients.[49] Other findings are ambiguous or have not been replicated.[46,48] The mechanisms remain obscure. Still, the serotonin findings may well be important and therefore the effects of halopemide on serotonergic mechanisms are of interest.

Halopemide hardly affects serotonin receptors. It is virtually inactive against either tryptamine-induced seizures or tremors in rats (ED50 > 160 mg/kg orally).[35] It has a relatively low potential in comparison to various neuroleptic drugs to displace ^{3}H-spiperone from serotonin-S_2 sites in rat frontal cortex (K_i = 220 n*M*).[51]

Blood platelets act in many ways like brain synaptosomes and have been proposed as a model for CNS serotonergic neurons.[47,48,52] We have tested the possible interference of halopemide with the uptake of serotonin in this model.[52] Halopemide and its putative (basic) metabolites R 38570 and R 29676 (Fig. 1) inhibit the uptake of serotonin by rat blood platelets in a dose-dependent manner, while *p*-fluorohippuric acid, another putative metabolite, is fully devoid of activity.[52] However, none of the tested compounds is more potent than imipramine. In particular halopemide is only weakly active (Table II).

In order to evaluate the influence on serotonin release, we have compared the effects of halopemide, haloperidol, spiperone and R 29800 on the spontaneous and potassium-induced release of serotonin, noradrenalin, acetylcholine and γ-aminobutyric acid (GABA) from rat cerebrocortical slices prelabelled with tritiated neurotransmitters *in vitro*.[53] Especially basal serotonin outflow is enhanced by halopemide and neuroleptic agents. This effect, which seems to be non-specific in nature, cannot be excluded to be of relevance *in vivo*. Halopemide tends to affect depolarization-induced serotonin efflux at lower concentrations than it affects the efflux of other neurotransmitters, but the results are hard to interpret and lack statistical significance.[53]

It is concluded, that halopemide might stimulate serotonergic neurotransmission *in vivo* by enhancing spontaneous serotonin efflux in addition to inhibition of the reuptake by its metabolites.[18] However, the evidence is far from conclusive. Whether this action is of clinical significance or not and whether it is related to its therapeutic effects in withdrawn, inactive patients, remains to be elucidated.

INTERACTION WITH GABA-ERGIC TRANSMISSION

There are several arguments, that modulation of the neurotransmitter function of γ-aminobutyric acid (GABA) – a major inhibitory transmitter in the brain – is of relevance for part of the (side) effects of neuroleptic drugs. Certain antipsychotic drugs are known to increase GABA turnover in discrete brain

TABLE II

Effects of halopemide and putative metabolites on serotonin and GABA uptake and on GABA and benzodiazepine binding

	Serotonin uptake*	GABA uptake*	GABA binding*	Benzodiazepine binding*	
Halopemide	600-700	15.1	incomplete	24.0	15.6
Putative metabolites					
R 29676	79	280	11.6	127	160
R 38570	57	≫100	15.9	217	52.2
p-fluorohippuric acid	n.i.†	n.i.	n.i.	n.i.	incomplete
Reference drugs					
spiperone	–‡	18.1	13.8	–	–
R 29800	–	19.8	2.9	–	–
imipramine	1.7	–	–	–	–
(+)-bicuculline	–	–	8.6	–	–
diazepam	–	–	–	0.004	–
Ligand		GABA	GABA	Flunitrazepam	Diazepam
K_m or K_d	0.52	5.65	0.02	0.001	0.007

* Median inhibitory concentrations (IC50), K_m or K_d in μ*M*.

† n.i. = no inhibition.

‡ – = not evaluated.

areas *in vivo*.[54 55] *In vitro* inhibition of ^{3}H-GABA uptake,[54 56-58] receptor binding[59] and release[58 60 61] by some, but not all neuroleptic agents has been demonstrated. The significance of these findings concerning the antipsychotic action is disputed, although the GABA system may be impaired in schizophrenia[62 63] and GABA-ergic drugs can elicit behavioural effects.[62 64 65] Moreover, GABA neurons are most intimately involved with dopaminergic transmission *inter alia* in a nigrostriatal feedback loop,[54 55 66] whereas GABA agonists potentiate and GABA antagonists inhibit neuroleptic-induced catalepsy[67 68] and GABA-ergic abnormalities may be related to extrapyramidal disorders.[54 59 61 63]

Halopemide, R 29800 and spiperone inhibit sodium-dependent GABA uptake by rat brain P_2 homogenates with median inhibitory concentrations (IC_{50}'s) of 15-20 μM.[69] Halopemides putative metabolites are markedly less or not active (Table II). GABA release from rat brain cerebrocortical slices is only affected by a high concentration of halopemide.[53 69] These properties suggest a GABA potentiating action. However, halopemide is almost equipotent to related neuroleptic agents and its metabolites do not enhance the GABA-mimetic action. Therefore, such an action is probably not directly related to the characteristic nature of halopemides clinical effects.

High-affinity sodium-independent ^{3}H-GABA binding to disrupted, Triton X-100 treated membranes ($GABA_2$ sites) is inhibited by halopemide. However, the effect is only observed at fairly high concentrations and inhibition is incomplete.[69] Its metabolites R 29676 and R 38570 are more active. GABA binding is inhibited equipotently by spiperone, R 29676, R 38570 and the GABA antagonist (+)-bicuculline (Table II). R 29800 is even more potent. We wanted to determine whether the actions of halopemide and its putative metabolites are GABA-agonistic or antagonistic in nature as the GABA receptor may have two conformational states, one preferentially binding agonists (like ^{3}H-GABA) and one preferentially binding antagonists (like ^{3}H-bicuculline).[70]

GABA-antagonistic properties may be related to halopemides psychotropic actions and its lack of parkinsonian side effects as it has been reported that the agonist muscimol potentiates stereotyped gnawing induced by methylphenidate and antagonizes the protective action of neuroleptics on this behaviour.[71] Directly and indirectly acting GABA antagonists also antagonize haloperidol-induced catalepsy.[67 68] As radiolabelled GABA antagonists were not available at that time, we used the *in vitro* model of GABA-ergic stimulation of benzodiazepine binding.[72]

At present it is well established that within the plasma membrane of neurons, there exists a highly integrated supramolecular protein complex termed the GABA/benzodiazepine receptor/chloride channel complex,[73-77] representing a multimer with a molecular weight of at least 500,000.[78] At least three distinct recognition sites are present within this complex: the $GABA_A$ receptor, the benzodiazepine receptor and a chloride gating mechanism (chloride channel or chloride ionophore). All the recognition sites within the complex can affect the recognition properties of all the other sites.[78] $GABA_A$ receptors represent a subset of GABA recognition sites which affect membrane potential by controlling the opening of the chloride ionophore.[75 76] Upon binding GABA the supramolecular complex undergoes a reversible conformational change, thereby causing brief opening of the chloride channel. The benzodiazepine receptor regulates the affinity state of $GABA_A$ receptors and/or the efficiency of the GABA-controlled channel opening. Benzodiazepines do not open chloride ionophores by themselves, but enhance the effects of GABA.[73-77]

As a consequence of the existence of the above mentioned complex, changes in the properties of the binding of ligands with affinity to $GABA_A$ recognition sites or to binding sites or to ^{35}S-*t*-butylbicyclophosphorothionate (TBPS) binding sites (^{35}S-TBPS labels one of the drug receptors of the $GABA_A$ regulated chloride ionophore) can be used to predict several of the pharmacologic properties from experiments *in vitro*.[79] Stimulation of $GABA_A$ receptors results in an enhanced affinity of benzodiazepine receptors for benzodiazepines.[72-75 77] This phenomenon offers a possibility to investigate agonist–antagonist interactions at GABA receptors in the CNS.[18 72] The ability of a drug with affinity to GABA binding sites to increase the binding of benzodiazepines clearly indicates GABA-agonistic properties. As we were interested to know whether the actions of halopemide are GABA-agonistic or antagonistic in nature, we studied its effects on GABA-modulated benzodiazepine binding. Neither halopemide nor its putative metabolites stimulate the binding of ^{3}H-diazepam to washed membranes.[72] The absence of facilitatory effects on benzodiazepine binding does not support agonistic GABA-ergic properties.

Quite surprisingly halopemide inhibits ^{3}H-benzodiazepine binding to crude and washed rat forebrain membranes with IC_{50} values of 16-25 μM.[72] Its putative metabolites are considerably less active (Table II). The K_i of halopemide is only slightly larger than that of some less active benzodiazepines.[18 72 80 81] Preliminary experiments have shown that its interaction may be of competitive nature. Neuroleptics of butyrophenone type are known to lack affinity to benzodiazepine binding sites.[18 80 81] We have concluded, that the inhibition of benzodiazepine binding by halopemide is not mediated via GABA receptors.[72] In spite of its relatively high median inhibitory concentrations, the effect may be of relevance *in vivo* as it has been shown that the strength with which a benzodiazepine binds *in vitro*

does not relate in practical terms to its potency *in vivo* as only part of the benzodiazepine receptors need to be occupied for a biological effect.[74]

Conclusions

In spite of its ability to displace ^{3}H-butyrophenones *in vitro*, halopemide does not interact with all dopamine receptors *in vivo* as its distribution profile differs from that of dopamine antagonists, both regionally and at a subcellular level. These findings are hard to explain, and are probably not a simple reflection of poor passage through the blood-brain barrier, although the latter might contribute to its deviating pharmacological profile. It is suggested, that of the effects of halopemide especially those on spontaneous serotonin release and on GABA and benzodiazepine binding sites (concomitantly) are of interest and merit further investigation.

Quite unique properties at a molecular level may be concluded from the ability of halopemide and its putative metabolites to affect both ^{3}H-GABA and ^{3}H-benzodiazepine binding. An explanation may be, that the affinity constants are coincidentally of similar magnitude, which would indicate mixed benzodiazepine- and GABA-like properties. It is also possible, that halopemide mimics the action of an endogenous inhibitor of $GABA_2$ sites (termed GABA modulin), which is reciprocally displaced by benzodiazepines.[73 77] Mimicry of GABA modulin would result in anti-GABA-ergic effects and could therefore be related to the lack of parkinsonian side effects. However, the nature and function of GABA modulin is not beyond debate.

During the last few years, various new ligands of the benzodiazepine receptor have been discovered.[82] Some of them induce a classical positive influence on the GABA receptor/channel function (full agonists), others have only minimal or no regulatory influence (full antagonists), and still others are in between (partial agonists). A new prototype of receptor ligands is formed by (partial) inverse agonists, which bind to benzodiazepine receptors, but produce effects diametrically opposed to those of full agonists (*e.g.* arousal).[75 82] These inverse agonists decrease the functional effects of GABA by reacting with receptors. It is tempting to speculate upon the intriguing possibility that halopemide might have such a partial inverse benzodiazepine-agonistic effect. Although evidence is far from complete, the effects of halopemide at a molecular level and its clinical properties, seem to be at least in part in agreement with such an action. In this context a comparison with the effects of (partial) inverse benzodiazepine agonists in autistic patients might be relevant. Unfortunately, these effects have not yet been investigated.

Halopemide is preferentially accumulated by the pituitary gland and within the CNS in the caudal part of the septal area and the striae medullares. Experiments elucidating the nature of the interaction within these areas are probably indicated.

In the plasma of man treated with halopemide, considerable amounts of R 29676 (but not R 38570) have been detected.[83] Therefore, investigations concerning the effects of both halopemide and R 29676 on GABA-ergic transmission within above-mentioned areas of the CNS and its neuroendocrinological effects merit highest priority.

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