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SPECIAL ISSUE

Johannes Kornhuber · Jens Wiltfang · Peter Riederer · Stefan Bleich

Neuroleptic drugs in the human brain

Clinical impact of persistence and region-specic distribution

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Abstract After discontinuation of neuroleptic agents, their effects are still present for a long time. The exact underlaying mechanisms are still unclear. In two previous studies we measured the concentrations and region-specific distribution of haloperidol (Kornhuber et al. 1999) and levomepromazine (Kornhuber et al. 2006) in postmortem human brain tissues. The aim of the present paper is to compare the results of these two studies. Even after short-term treatment, haloperidol and levomepromazine concentrations reach high levels in human brain tissue. Haloperidol concentrations in brain tissue are 10–30 times higher than the optimum serum concentrations in the treatment of schizophrenia. The brain-to-blood concentration ratio of levomepromazine is about 10. The estimated elimination half-life of these drugs in brain tissue are 6.8 days (haloperidol), 7.9 days (levomepromazine) and 27.8 days for the metabolite desmethyl-levomepromazine, respectively. After two half-lives (about 2 weeks), a considerable amount of drug remains in brain tissue. Haloperidol concentrations appeared to be homogeneously distributed across different brain areas, whereas levomepromazine shows a region-specific distribution, with highest values in the basal ganglia. The persistence of neuroleptic drugs in the human brain might explain their prolonged effects and side effects. The region-specific distribution of levomepromazine may increase our understanding of both the preferential toxicity of neuroleptic drugs against basal ganglia structures and higher basal ganglia volumes in patients treated with neuroleptics.

Key words human · postmortem brain · pharmacokinetics · haloperidol · levomepromazine · neuroleptic drug · region-specific distribution

J. Kornhuber, MD (✉) · J. Wiltfang · S. Bleich
Department of Psychiatry and Psychotherapy
Friedrich-Alexander-University of Erlangen-Nuremberg
Schwabachanlage 6
91054 Erlangen, Germany
Tel.: +49-9131/853-4160
Fax: +49-9131/853-4862
E-Mail: johannes.kornhuber@psych.imed.uni-erlangen.de

P. Riederer
Department of Psychiatry
University of Würzburg
Germany

EAPCN 661

Introduction

Side effects such as parkinsonian symptoms or neuroleptic malignant syndrome may persist for several weeks after discontinuation of neuroleptic drugs and psychotic patients may not relapse for weeks or months after withdrawal of neuroleptic treatment (Addonizio et al. 1987; Kornhuber and Weller 1994; Viguera et al. 1997). The exact underlaying mechanisms of these prolonged effects are still unclear and, despite their extensive clinical use, little is known about the cumulation, elimination half-life and regional distribution of neuroleptics, especially in human brain tissue.

It has been shown in rats (Cohen et al. 1992; Tsuneizumi et al. 1992; Baldessarini et al. 1993; Squires and Saederup 1997; Weigmann et al. 1999; Gemperle et al. 2003) as well as in humans (Korpi et al. 1984) that brain concentrations of neuroleptic drugs after applications of therapeutic doses were 20 to 100 times higher than the corresponding plasma levels. In previous studies we looked at the brain concentrations, the regional distribution and the elimination half-lifes of haloperidol (Kornhuber et al. 1999) and levomepromazine (Kornhuber et al. 2006). The results of both studies will be summarized and compared here.

The haloperidol and levomepromazine studies

The present article provides a summary report of two previous studies (Kornhuber et al. 1999; Kornhuber

et al. 2006) (Table 1). The methodology of the two studies was similar: In both studies, brain tissue was obtained from the Austrian-German Brain Bank Wuerzburg. Postmortem handling of the autopsy material was similar in all cases and was performed according to a standardized procedure (Gsell et al. 1993). Brain tissue was taken at autopsy from 15 subjects (haloperidol: n = 11, 7 females, 4 males; levomepromazine: n = 5, 4 females, 1 male; one patient who had been treated with haloperidol and levomepromazine was investigated in both studies) who had been treated orally with these neuroleptics. The brains were collected between 1987 and 1994 (Table 1). In the Haloperidol-Study, tissue samples were taken from several different brain regions from both sides of the brain: temporal cortex, cingulated gyrus, caudate nucleus, dentate nucleus, corpus callosum, and other brain regions. In the Levomepromazine-Study, tissue samples were taken from 17 to 43 different brain regions. It was not possible to investigate tissue samples of all these regions from every brain. Therefore, in the Levomepromazine-Study several smaller brain regions were grouped to form larger brain areas (Kornhuber et al. 2006).

Drug concentrations were measured with an HPLC method. Since there was only a single measurement per individual in various brain regions and not sufficient data to describe the pharmacokinetic profile in each individual patient, a population pharmacokinetic analysis was performed using the computer software program NONMEM (Beal and Sheiner 1992). The aim of this analysis was to estimate the average elimination half-life of haloperidol, levomepromazine and desmethyl-levomepromazine in brain tissue in the population of patients investigated. Mean values are given ± SD. Further details of the laboratory and statistical analyses are published in (Kornhuber et al. 1999; Kornhuber et al. 2006).

Haloperidol was detected in the brain tissue of all patients previously treated with the drug, with concentrations ranging from 8.9 ng/g (caudate nucleus) to 226.7 ng/g (temporal cortex). Haloperidol concentrations appeared to be homogeneously distributed across different brain areas within a single individual. To investigate interindividual differences, mean values of haloperidol concentrations were calculated for every patient. In contrast to the intraindividual differences between several brain regions, the interindividual differences between patients were considerable. The highest mean haloperidol concentration was found in a patient on a relatively high dose of haloperidol that had been given until death. Low concentrations in brain tissue were found when haloperidol had been withdrawn for more than a week. There was no apparent relation between duration of treatment and mean haloperidol concentration (Figure 1B). Even after treatment for only 3 days, considerable brain concentrations were measured. Higher doses of haloperidol seemed to be related to higher concentrations in brain tissue (Figure 1C). The brain concentration decreased within days after drug withdrawal (Figure 1D). In the population kinetic analysis with NONMEM (Figure 1D, inset) a brain elimination half-life of 6.8 days was calculated for the mean subject.

Levomepromazine concentrations in patients previously treated with the drug, ranged from 36 ng/g (plexus choroideus) to 858 ng/g (putamen, pars posterior). Desmethyl-levomepromazine concentrations ranged from 17 ng/g (corpus mamillare) to 1472 ng/g (nucleus medialis thalami). With the repeated measurement ANOVA, levomepromazine concentration was region-specific ($F = 4.43$, $P = 0.013$), with highest concentrations in the basal ganglia and lowest concentrations in the cortex (Figure 2) (significant difference between cortex vs. basal ganglia ($P < 0.05$) with the post-hoc Scheffé test). A parallel situation was observed with desmethyl-levomepromazine concentrations; however this did not reach statistical significance (ANOVA, $F = 2.02$, $P = 0.14$). The ratio between levomepromazine and desmethyl-levomepromazine did not exhibit a region-specific distribution. The interindividual differences between patients were considerable. There was no apparent relationship between duration of treatment and mean levomepromazine concentration. Even after treatment over only 3 days, considerable brain concentrations were measured (data not shown). In the population kinetic analysis using NONMEM a brain-elimination half-life of 7.9 days for levomepromazine and 27.8 days for desmethyl-levomepromazine were calculated for the mean subject.

Table 1 Data of patients with haloperidol and levomepromazine treatment

	Haloperidol Study	Levomepromazine Study
Patients age range (years)	47.9–94.4	71.8–94.4
Number of Patients	11 (m, f)	5 (m, f)
Postmortem interval (hrs)	3.5–40.7	3.6–40.7
Daily oral dose (mg)	0.5–15	6.25–37.5
Duration of treatment (days)	3–581	1–1607
Drug-free time (days)	0.1–15.6	0.2–16.5
Collection of brains between years	1989–1994	1987–1994
Duration of storage of brain tissue at low temperature (years)	2.2–7.1	4–11

The drug-free time was calculated as the difference between time of last intake of the drug and time of death; the postmortem time was calculated as the difference between time of death and freezing of brain tissue. One patient who had been treated with haloperidol and levomepromazine was investigated in both studies. Data are taken from (Kornhuber et al. 1999; Kornhuber et al. 2006)

Discussion

Brain-to-blood ratio of neuroleptic drugs

Haloperidol and levomepromazine are weak bases and amphiphilic substances. With these physico-

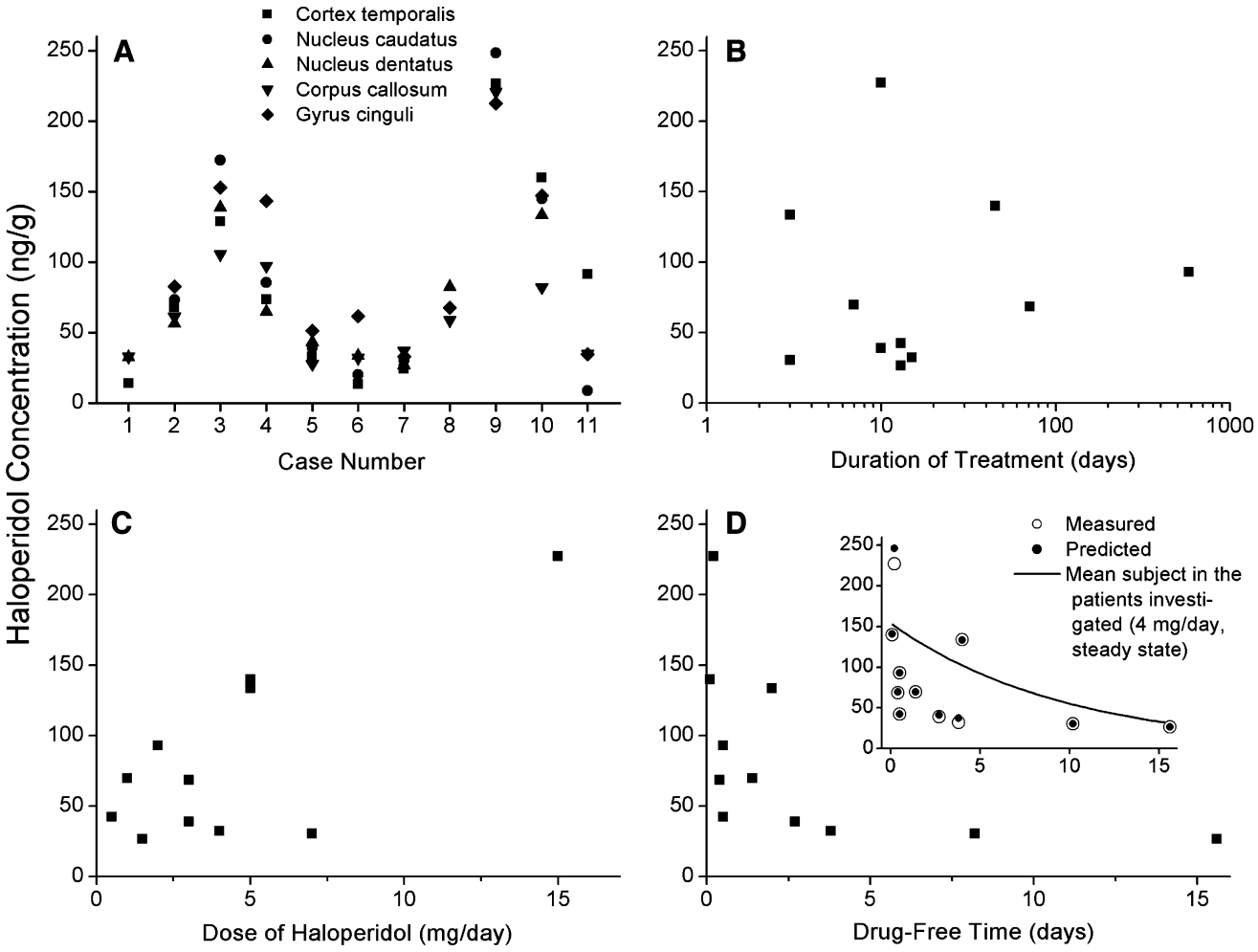

Fig. 1 Haloperidol concentration in postmortem human brain tissue. Reproduced with permission from (Kornhuber et al. 1999). **A**: Haloperidol concentrations in individual brain areas in the cases investigated are shown. While the interindividual variance is considerable, the intraindividual differences between brain areas are small. In parts B, C, and D, mean values of haloperidol concentration are given for each patient. **B**: Duration of haloperidol treatment had no apparent impact on mean haloperidol concentration in brain tissue. **C**: Mean haloperidol concentration in brain tissue increased with dose of drug. The relatively low haloperidol concentration in the patient with 7 mg/day might be related to a short duration of treatment and a long drug-free time. **D**: There was a clear decay of mean haloperidol concentration in brain tissue with increasing drug-free time. Even 15 days after withdrawal, mean haloperidol concentration in brain tissue was about 26 ng/g, which is in the order of therapeutically relevant plasma concentrations. The inset shows the results of the population kinetic analysis with the measured and predicted mean haloperidol concentrations. The curve gives the estimated haloperidol concentration of the mean subject in the study group, assuming steady-state conditions and a daily dose of 4 mg. The calculated half-life of haloperidol in brain tissue is 6.8 days.

chemical characteristics, accumulation in brain tissue is mainly due to solution in lipophilic structures and trapping in acidic intracellular compartments like lysosomes (Kornhuber et al. 1995b; Daniel and Wójcikowski 1997). As a whole, it has been shown that lysosomal trapping is an important factor determining the distribution of the basic lipophilic psychotropics, whereas their tissue uptake depends more on phospholipid binding than on lysosomal trapping. This latter trapping is believed to be involved in the pharmacokinetic interactions between psychotropic drugs (Daniel and Wójcikowski 1997).

When the concentrations measured in human brain tissue are compared with clinically effective plasma haloperidol levels reported in the literature (McEvoy et al. 1991; Volavka et al. 1995), the brain-to-blood concentration ratio in humans is about 10–30, even after short-term treatment. Similar concentration ratios were reported previously in two subjects (Korpi et al. 1984). These results are paralleled in animal experiments. A brain-to-blood concentration ratio of 22 for haloperidol was found in rats both after a single dose (Sunderland and Cohen 1987) and after subchronic administration (Tsuneizumi et al. 1992).

When comparing the brain concentrations with plasma levomepromazine levels reported in the literature (Dahl 1976; Dahl et al. 1977; Tokunaga et al. 1997), the brain-to-blood concentration ratio for levomepromazine is about 10 even after short-term treatment. These results are also paralleled in animal experiments showing brain-to-blood concentration ratios of 17–33 in the rat (Afifi and Way 1968).

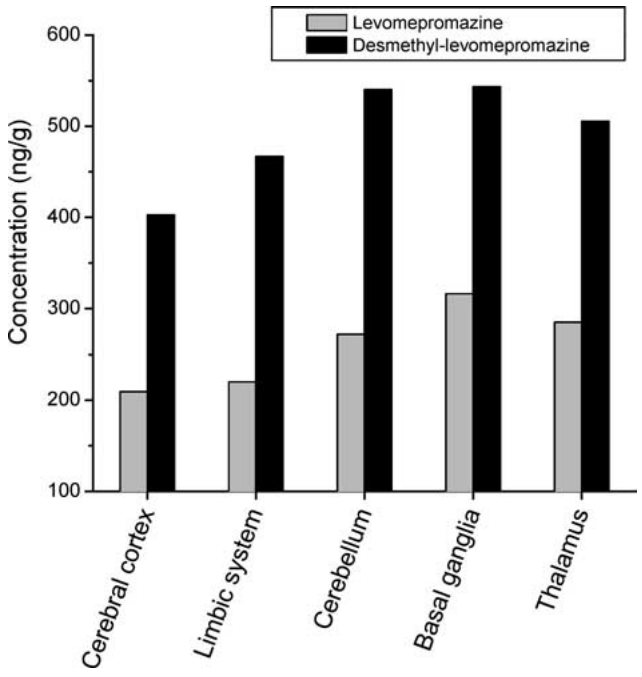

Fig. 2 Regional distribution of levomepromazine and desmethyl-levomepromazine in human brain tissue. Several smaller brain regions were combined to calculate a mean value for a larger brain area. The dataset contained 5 cases with 5 larger brain areas each. A repeated measurement ANOVA reveals a region-specific distribution of levomepromazine in the human brain, with a significant difference between the cortex and the basal ganglia (for further details see text). The figure is taken from (Kornhuber et al 2006).

Rapid cumulation of neuroleptic drugs in human brain tissue

It has been hypothesized that the therapeutic delay of antidepressant and neuroleptic drugs might be related to a slow uptake of the drug into human brain tissue (Kornhuber et al. 1995b). A slow uptake has been found for amantadine in postmortem human brain tissue (Kornhuber et al. 1995a) and for fluoxetine *in vivo* (Karson et al. 1993). We did not find a slow uptake for haloperidol. Even after 3 days of treatment with haloperidol, the concentration in brain tissue was comparable to that for long-term treatment. This indicates that haloperidol rapidly accumulates in brain tissue. Similarly to haloperidol, considerable levomepromazine concentrations were found in the human brain even after a single application of the drug. The rapid cumulation of neuroleptic drugs is unexpected, because drugs with an elimination half-life of about one week should reach a steady-state concentration over several weeks. The acidotropism of these drugs might help to explain this phenomenon.

Persistence of neuroleptic drugs in human brain tissue

The brain elimination half-life of haloperidol is about 1 week (6.8 days). After two half-lives (about 2 weeks) there is still a considerable amount of haloperidol in brain tissue. A comparably long elimination half-life was found for levomepromazine and its metabolite desmethyl-levomepromazine.

For haloperidol, there is evidence of a long elimination half-life from in-vivo PET measurements (Farde et al. 1988). In a brain series of patients treated with different neuroleptic drugs there is also evidence of long elimination half-lives, using the dissociation constant (K_d) values for the D_2 receptor as a measure of residual neuroleptic drug at the receptor (Kornhuber et al. 1989).

The estimated elimination half-life of haloperidol from human brain tissue is in close agreement with values derived from the measurement of brain haloperidol concentrations (Öhman et al. 1977; Cohen et al. 1992) and antidopaminergic effects (Campbell et al. 1985; Cohen et al. 1992) in experimental animals. The elimination half-life appears to be longer in brain tissue compared with serum values, even when one is examining terminal elimination half-lives of haloperidol (Ereshefsky et al. 1986; Hubbard et al. 1987).

Region-specific distribution of neuroleptic drugs in human brain

Haloperidol concentrations appeared to be homogeneously distributed across different brain areas within a single individual. Similar results have been obtained within the rat brain, where no relevant differences in the concentration of haloperidol between the striatum, limbic system, and cerebellum after a single intraperitoneal injection were found (Öhman et al. 1977). On the other hand, in experimental animals, a preferential accumulation of butyrophenones in brain areas with a large dopamine concentration has previously been suggested (Janssen et al. 1968; Laduron et al. 1978; Korpi et al. 1984).

In the Levomepromazine-Study (Kornhuber et al. 2006) for the first time, a region-specific distribution of a neuroleptic drug has been determined in the human brain showing high levomepromazine concentrations in basal ganglia and the thalamus. The reasons for region-specific accumulation of levomepromazine in human brain tissue are not fully understood. Since metabolic enzymes for xenobiotics have a region-specific distribution in the brain (Britto and Wedlund 1992; Schilter and Omiecinski 1993; Ravindranath et al. 1995; Norris et al. 1996), region-specific metabolization of levomepromazine (Hals and Dahl 1994) may also contribute to region-specific differences in tissue sequestration. Phenothiazines are hydroxylated by Cyp2D6 (Meyer et al. 1996b). Compared to the neocortex, hippocampus und cerebellum, the Cyp2D6 activity is low in the basal ganglia of the human brain (Siegle et al., 2001). Haloperidol, on the other hand, is only a weak CYP2D6 ligand (Meyer et al. 1996a; Daniel et al. 2005). Thus, low expression of CYP2D6 in the basal ganglia of the human brain

Table 2 Comparison of the findings of haloperidol and levomepromazine measurements in human brain tissue

	Haloperidol Study	Levomepromazine Study
Blood-to-brain concentration ratio	10–30	10
Rapid appearance in brain tissue	yes	yes
Elimination half-life in brain tissue (days)	6.8	7.9
Region-specific distribution	No	Higher concentrations in basal ganglia

Data are taken from (Kornhuber et al 1999; Kornhuber et al 2005)

might contribute to the region-specific distribution of levomepromazine, while less affecting the regional distribution of haloperidol. Further studies are necessary to clarify the causes of region-specific distribution of some but not all neuroleptic drugs in human brain tissue.

Clinical impact

Overall, the pharmacokinetic properties of haloperidol and levomepromazine are similar (Table 2). Both exhibit a brain-to-blood concentration ratio of about 10 or more, both show a rapid sequestration in the human brain, both show an elimination half-life of about one week or more. However, there are differences regarding region-specific distribution which might be explained by the region-specific distribution of the expression of CYP2D6 in the human brain.

Sequestration of haloperidol and levomepromazine in lipophilic and acidic intracellular compartments might induce a wide range of changes in neuronal morphology and function. While such changes have not yet been investigated directly for haloperidol and levomepromazine, reports are available for other neuroleptic drugs, antidepressant drugs or opiates regarding subcellular structure (Bal and Smialowska 1987; Bal-Klara and Bird 1990; Sklair-Tavron et al. 1996), cell volume (Hoffmann and Simonsen 1989; Hara et al. 1999) and neuronal function (Kornhuber et al. 1995b). Considering the potential changes in neuronal structure and function, the non-specific cumulation of haloperidol and especially the region-specific accumulation of levomepromazine in human brain tissue might have parallels to several findings in patients treated with neuroleptics, specifically basal ganglia enlargement and tardive dyskinesia. Neuroleptic-induced basal ganglia enlargements in schizophrenia have been repeatedly described both in postmortem brain (Heckers et al. 1991) and *in vivo* MRI (Chakos et al. 1995; Gur et al. 1998) studies, in non-schizophrenic psychiatric illness (Doraiswamy et al. 1995) and in rat models (Chakos et al. 1998). The preferential accumulation of a neuroleptic drug in basal ganglia, might help to understand this phenomenon.

During long-term therapy with neuroleptic drugs, about 30% of the patients develop tardive dyskinesia, which remains as a chronic disease after withdrawal of the drug in a significant portion of the patients. The cause of tardive dyskinesia has been associated with neurotoxic properties of neuroleptic drugs. Basal ganglia appear to be particularly vulnerable against the neurotoxic action of neuroleptic drugs (Gunne et al. 1984). Higher concentrations of neuroleptic drugs in certain brain areas might lead to apoptosis or necrosis and might thus explain the regional differences in neuronal vulnerability, i.e. cell death due to prolonged administration of neuroleptic drugs in basal ganglia associated with tardive dyskinesia. The molecular mechanisms of neuroleptic-induced cell death might include oxidative stress (Kropp et al. 2005), shifts in pH-balance and toxic effects of metabolites.

Furthermore, it has been suggested that basal ganglia volume enlargement correlates with tardive dyskinesia (Chakos et al. 1998). The high concentrations and the long half-life of both haloperidol (Kornhuber et al. 1999) and especially the region-specific distribution of levomepromazine (Kornhuber et al. 2006) in human brain tissue suggests that neurotoxic metabolites may be present in brain tissue for several weeks, even after short-term treatment.

The elimination half-life of both neuroleptic drugs is around one week. The overall effect is illustrated in Figure 3: Even after short-term treatment, neuroleptic drugs rapidly appear in human brain tissue, reach high brain-to-blood concentrations and, upon withdrawal of neuroleptic drugs, are slowly released from brain tissue. The released neuroleptic drug reaches receptors in cell membranes and results in long-lasting effects and side-effects.

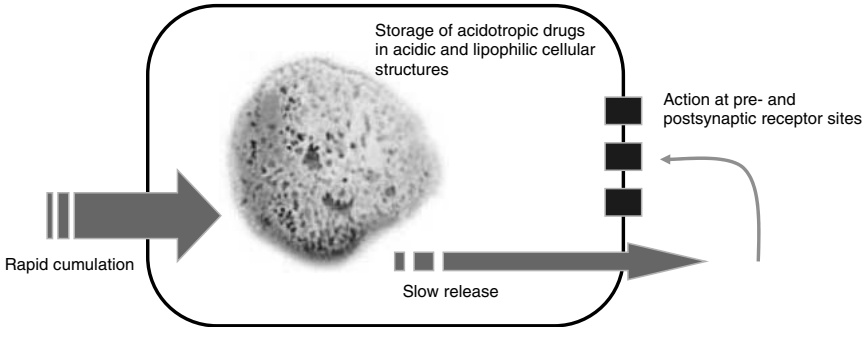

Fig. 3 Model for uptake, storage, release and long-acting receptor effects of neuroleptic drugs. Due to acidotropy and lipophilicity, neuroleptic drugs reach high brain-to-blood concentration ratios. These drugs are stored in acidic intracellular compartments and cell membranes, indicated by the sponge. Neuroleptic drugs reach high concentrations within a short time and are characterized by a long elimination half-life. This model explains the long-lasting effects of neuroleptic drugs after withdrawal.

Conclusion

There is evidence of a high blood-to-brain concentration ratio for both haloperidol and levomepromazine. The estimated elimination half-lives of these drugs in brain tissue are 6.8 days for haloperidol, 7.9 days for levomepromazine) and 27.8 days for its metabolite desmethyl-levomepromazine. After two half-lives (about 2 weeks) there is still a considerable amount in brain tissue.

Side effects such as parkinsonian symptoms or neuroleptic malignant syndrome may persist for several weeks after discontinuation of neuroleptic drugs and relapse in psychotic patients may not occur for weeks or months after withdrawal of neuroleptic treatment. The persistence of neuroleptic drugs in the human brain might explain their long-term effects as well as side-effects.

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