Review

The neuropathological effects of antipsychotic drugs

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Abstract

In addition to their neurochemical effects, antipsychotic (neuroleptic) drugs produce structural brain changes. This property is relevant not only for understanding the drugs' mode of action, but because it complicates morphological studies of schizophrenia. Here the histological neuropathological effects of antipsychotics are reviewed, together with brief mention of those produced by other treatments sometimes used in schizophrenia (electroconvulsive shock, lithium and antidepressants). Most data come from drug-treated rats, though there are also some human post-mortem studies with broadly congruent findings.

The main alteration associated with antipsychotic medication concerns the ultrastructure and proportion of synaptic subpopulations in the caudate nucleus. In rats, synapses and dendrites in lamina VI of the prefrontal cortex are also affected. The changes are indicative of a drug-induced synaptic plasticity, although the underlying mechanisms are poorly understood. Similarly, it is unclear whether the neuropathological features relate primarily to the therapeutic action of antipsychotics or, more likely, to their predisposition to cause tardive dyskinesia and other motor side-effects. Clozapine seems to cause lesser and somewhat different alterations than do typical antipsychotics, albeit based on few data. There is no good evidence that antipsychotics cause neuronal loss or gliosis, nor that they promote neurofibrillary tangle formation or other features of Alzheimer's disease. © 1999 Elsevier Science B.V. All rights reserved.

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1. Introduction

Antipsychotics affect many neurotransmitter systems. Whatever the therapeutic significance of these adaptations, their occurrence makes antipsychotic drugs an important and well-recognised potential confounder of neurochemical studies of schizophrenia. Though less well documented, antipsychotics also affect brain structure. Recent imaging studies have provided convincing evidence

for striatal enlargement in drug-treated patients (Keshavan et al., 1994; Chakos et al., 1994, 1995; Doraiswamy et al., 1995) and rats (Chakos et al., 1998). There are also single reports suggesting that antipsychotic dose is correlated with progressive brain atrophy (Madsen et al., 1998) and increasing thalamic volume (Gur et al., 1998). These macroscopic effects are consistent with a range of morphometric alterations in neurons and synapses in the striatum and elsewhere documented over the past 20 years or so. The significance of these observations is twofold. Firstly, they may contribute to the therapeutic or side-effect profile of the

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drugs (Jeste et al., 1998). Secondly, as with neuro-chemical studies, any neuropathology resulting from antipsychotic treatment may confound the search for the neuropathology of psychosis itself. This article reviews the literature concerning the histological effects of antipsychotic medication. It also briefly summarises the known neuropatholog-ical consequences of certain other therapies which are or have been used in schizophrenia.

2. Neuropathological effects of antipsychotics: ways to approach the problem

As nearly all patients in contemporary neuro-pathological studies of schizophrenia have received antipsychotics, comparison of drug-naive and treated subjects is not feasible (and one would worry that the former were unrepresentative in other respects anyway). Use of archival material from the pre-antipsychotic era can be valuable, but it is sparse and suffers from problems of diagnosis, as well as its mode of processing and duration of storage, which hamper many tech-niques. Hence several other strategies have been adopted to investigate whether antipsychotics pro-duce neuropathological effects:

(a) Comparison of patients on medication at death with those who had been drug-free for a significant period. Drawbacks include the assump-tion that medication effects on brain structure are reversible within the time frame, and that the two groups are otherwise clinically and pathophysio-logically comparable.

(b) Calculation of life-time medication history, usually converted to chlorpromazine dose equiva-lents, and correlation of total exposure with the parameter in question. This approach assumes a cumulative and linear relationship between the variables, and one in which treatment many decades ago is given equal weight to that received recently.

(c) Use of an antipsychotic-treated non-schizo-phrenia control group. This usually comprises cases of dementia with psychosis, delusional disor-der, and/or bipolar disorder. Although such a group goes some way towards controlling for drug effects, their medication histories rarely approach

the duration and amount received by schizo-phrenics. Moreover, utilising cases with degenera-tive disorders adds its own neuropathological complications, whilst including paranoid or affec-tive psychoses begs the question of whether or not they share intrinsic pathological features with schizophrenia.

(d) Experimental studies in animals. These have many methodological attractions, but are subject to the reservations inherent in extrapolation of results between species.

(e) Investigation of the brains of antipsychotic-treated human subjects regardless of diagnosis.

Most neuropathological studies of schizo-phrenia have included one or more of approaches (a)–(c) to investigate the effects of antipsychotic medication. As a rule, no demonstrable confound-ing by the drugs has been seen, and they are not discussed further (see Harrison, 1999). Instead, the focus here is on studies in categories (d) and (e) which have directly investigated the neuropa-thology of antipsychotic administration.

3. Rat studies

Experimental studies of the neuropathological effects of antipsychotic drugs have concentrated on the ultrastructure and numerical density of neurons and synapses in rats.

3.1. Effects of antipsychotics on neurons

Table 1 summarises the results of the few studies which have examined neuronal size and density following administration of antipsychotics. In the striatum, there is a decreased packing density (Pakkenberg et al., 1973; Nielsen and Lyon, 1978; Jeste et al., 1992), though this likely reflects the striatal enlargement (Chakos et al., 1998) rather than a loss of neurons. Striatal neuron size may be increased (Benes et al., 1985a), probably a correlate of the synaptic plasticity occurring in this region (see Sections 3.2 and 3.3). Important nega-tive findings include the lack of effect of antipsy-chotics on the morphology or number of dopaminergic substantia nigra neurons (Gerlach, 1975; Benes et al., 1983) or on cortical neurons

Table 1
Animal studies[a] of antipsychotic drug effects on neurons

Study	Drug, dose and duration[b]	Parameters measured	Significant changes in drug-treated animals
Pakkenberg et al., 1973	Perphenazine enanthate, 3.4 mg/kg/2 w i.m. for 12 m	Neuronal density in cortex and striatum	20% reduction in striatum; no change in cortex[c]
Gerlach, 1975	Group 1: as above[d]. Group 2: 40 mg/kg/2 w i.m. for 6 m	Neuronal density in substantia nigra	No changes[c]
Fog et al., 1976	Perphenazine enanthate, 40 mg/kg/2 w i.m. for 6 m[e]	Neuronal density in cortex and striatum	No changes
Nielsen and Lyon, 1978	Flupenthixol decanoate, 4 mg/kg/w i.m. for 36 w; killed 14–18 w later	Neuronal density in striatum	10% cell loss in ventrolateral compared to dorsomedial sector
Benes et al., 1983	Haloperidol 3 mg/kg/d i.m. for 16 w	Neuronal density and size in substantia nigra pars compacta	No changes
Benes et al., 1985a	Haloperidol 3 mg/kg/d i.m. for 16 w[f]	Neuronal density and size in caudate	13% increase in neuronal size; density unchanged
Benes et al., 1985b	Haloperidol 3 mg/kg/d i.m. for 16 w[f]	Neuronal density and size in medial prefrontal cortex	No changes
Jeste et al., 1992	Fluphenazine decanoate, 5 mg/kg/2 w i.m. for 4, 8 or 12 m, killed 4–9 w later	Neuronal density in striatum	Decreased density of large neurons, only after 8 m treatment
Dawirs et al., 1998	Haloperidol, 5 mg/kg, 4 doses over 24 h	BrdU[g] labelling of dentate gyrus granule cells	Increased labelling, indicative of dividing cells (neurogenesis)
Jeste et al., 1998	Fluphenazine decanoate, 5 mg/kg/2 w i.m. for 4 m, killed 4 w later	Neuronal density in central striatum	No changes[h]

[a] All studies were carried out in rats, except Dawirs et al., 1998 (gerbils).

[b] d: days; w: weeks; m: months; i.m.: intramuscular injection.

[c] Comment also made on morphology and arrangement of neurons and glia; no differences were observed in treated animals.

[d] The same animals as used in Pakkenberg et al. (1973).

[e] Same animals as used in group 2 of Gerlach (1975).

[f] Apparently the same animals as used in Benes et al. (1983).

[g] 5′-Bromo-2′-desoxyuridine.

[h] Three age groups of rats treated; trend towards decreased density of large neurons in elderly rats.

(Pakkenberg et al., 1973; Fog et al., 1976; Benes et al., 1985b).

3.2. Effects of antipsychotics on synapses

Antipsychotic effects on synapses have been examined in greater detail than those upon neurons, and more significant alterations identified. The majority of studies have used electron microscopy, though more recently molecular markers of synapses (Section 3.3) have been applied. The methods each have advantages and disadvantages: electron microscopy allows direct visualisation and measurements of the structure of interest, but is time-consuming, limited to very small areas, and comparable measurements in human brain are problematic. The newer approaches are molecularly specific, make large-scale and anatomically widespread analyses feasible, and can be adapted more readily to post-mortem tissue; on the other hand they are only proxies and the underlying ultrastructural change has to be inferred.

Table 2 summarises the electron microscopy studies of antipsychotic treatment. Together they provide good evidence for altered synaptic ultrastructure in the striatum and, to a lesser extent, in frontal cortex of rats treated chronically with antipsychotics. The findings concern a change in

Table 2
Animal studies[a] of antipsychotic drug effects on synaptic ultrastructure

Study	Drug, dose and duration[b]	Parameters measured	Significant changes in drug-treated animals
Benes et al., 1983	Haloperidol 3 mg/kg/d i.m. for 16 w	Substantia nigra: number and area of axon terminals, dendrites and spines; number of synaptic vesicles	Increased axon terminals per dendrite
Benes et al., 1985a	Haloperidol 3 mg/kg/d i.m. for 16 w	As above, in caudate	Increase in size of asymmetric terminals and dendritic shafts
Benes et al., 1985b	Haloperidol 3 mg/kg/d i.m. for 16 w	As above, in layer VI of medial prefrontal cortex	Loss of dendritic spines and associated asymmetrical synapses; increase in other axon terminals. No other changes
Takeichi, 1985	Chlorpromazine 20 mg/kg/d p.o. for 15 m	Striatum: number, size and shape of vesicles in axospinous synapses	Small increase in vesicular size. Number and shape unchanged.
Ihara et al., 1986	Haloperidol 5mg/kg/d i.m. for 13d, killed 8d or 36d later	Striatum: number and area of putative dopamine terminals and vesicles	Decreased number of boutons and vesicles at both timepoints
Klintzova et al., 1989	Haloperidol 0.1 mg/kg/d i.m. for 3 w	Prefrontal cortex lamina VI: density of axodendritic and axospinous synapses; number, area and mitochondrial content of axon terminals; number and density of vesicles	Increased axodendritic but decreased axospinous synapses. Axodendritic synapses have reduced axon terminal area and fewer mitochondria; post-synaptic densities longer. Axospinous synapses have minor changes
Meshul and Casey, 1989	Haloperidol 0.5 mg/kg/d i.m. for 2 w, killed 1 d or 2 w later	Caudate and nucleus accumbens: number of synapses and those with PPD[b]; area of axon terminals	Reversible increase in synapses with PPD in caudate nucleus. No other changes
Uranova et al., 1991	Haloperidol 1 mg/kg/d i.m. for 3 w	Caudate and hippocampus (CA1): parameters as in Klintzova et al. (1989)	Caudate: increased axodendritic and axospinous synapses. Axospinous synapses have larger axon terminals with more mitochondria, larger size of post-synaptic density. Axodendritic synapses: smaller axon terminals with less mitochondria. No changes in hippocampus
Vincent et al., 1991	Haloperidol 1.3 mg/kg/d or clozapine 27 mg/kg/d p.o. for 12 m	Layer VI of prefrontal cortex: size of dendrites, spines and axon terminals; vesicle density; symmetric and asymmetric synapses	Haloperidol: reduced calibre of dendrites. Both groups: relative increase of symmetric axodendritic synapses. Clozapine: increase in the small number of symmetric axospinous synapses. No change in vesicle density or size of axon terminals
Kerns et al., 1992	Haloperidol 1.25 mg/kg/d i.m. for 24 d, killed 4 d later	Striatum: synapses, dendritic spines, synapses with PPD, myelinated axons	Increased density of spines and synapses, with trend for increase in synapses with PPD
Meshul et al., 1992	Haloperidol 0.5 mg/kg/d or clozapine 35 mg/kg/d i.m. for 2 w	Caudate, nucleus accumbens and layer VI of prefrontal cortex: number of synapses and those with PPD	Caudate: increased number of synapses with PPD after haloperidol. No changes elsewhere or with clozapine
See et al., 1992	Haloperidol or raclopride, 7 mg/kg/w i.m. for 7 m	Caudate: synapses with PPD	Increased number after either drug
Roberts et al., 1995	Haloperidol 1.5 mg/kg/d p.o. for 6 m, killed 1 d or 4 w later	Striatum: synaptic density, mitochondrial size, area and number	Decreased density of asymmetric axospinous synapses. Symmetric and axodendritic synapses unaffected. Increased mitochondrial size and decreased number. All changes reversed 4 w later, except loss of mitochondria
Meshul et al., 1996b	Haloperidol decanoate 38 mg/kg i.m. monthly for 12 m	Caudate: synaptic density, synapses with PPD	Asymmetric synapses decreased in density, but enlarged and increased proportion with PPD.
Kelley et al., 1997	Haloperidol 1.5 mg/kg/d p.o for 6 m, killed 1 d or 4 w later[c]	Striatum: dendritic spine size and density	Spine size unaffected. Spine density decreased and remained decreased 4 w later

[a] All studies carried out in rats.

[b] d: days; w: weeks; m: months. i.m.: intramuscular injection; p.o.: orally; PPD: perforated.

[c] The same animals as in Roberts et al. (1995).

the distribution and abundance of synaptic types, defined in terms of their cellular location (e.g., axodendritic vs axospinous; Klintzova et al., 1989; Uranova et al., 1991; Roberts et al., 1995), their appearance (e.g., asymmetrical vs symmetrical; Benes et al., 1985b; Vincent et al., 1991; Roberts et al., 1995) or the presence of structural specialisations (e.g., perforated postsynaptic densities; Klintzova et al., 1989; Meshul and Casey, 1989; Kerns et al., 1992; See et al., 1992; Meshul et al., 1992, 1996b). Alterations in the size (Benes et al., 1985a; Uranova et al., 1991) or content (Takeichi, 1985; Ihara et al., 1986; Klintzova et al., 1989; Uranova et al., 1991; Roberts et al., 1995) of axon terminals and dendrites (Benes et al., 1985b; Vincent et al., 1991; Kerns et al., 1992; Kelley et al., 1997) have also been described. Most (Meshul and Casey, 1989; Roberts et al., 1995) but not all (Roberts et al., 1995; Kelley et al., 1997) of the changes reverse within weeks of stopping the drugs, along with rebound changes in some parameters (Meshul and Tan, 1994; Meshul et al., 1996a). Also, although the data are sparse, clozapine appears to have different and lesser effects compared with haloperidol or the other typical antipsychotics investigated (Vincent et al., 1991; Meshul et al., 1992; P.J. Harrison and S.L. Eastwood, unpublished observations).

Although it is difficult to ascertain the overall pattern of synaptic alteration, consideration of the studies in Table 2 suggests that antipsychotics increase the proportion of symmetric and axodendritic synapses at the expense of asymmetric and axospinous ones (Benes et al., 1985b; Klintzova et al., 1989; Vincent et al., 1991; Roberts et al., 1995; Meshul et al., 1996b; cf. Kerns et al., 1992; See et al., 1992). This pattern implies that antipsychotics produce an altered numerical balance in favour of inhibitory synapses, given that asymmetric and axospinous synapses are largely glutamatergic and hence excitatory [Meshul et al., 1994; Peters and Palay, 1996]. However, the studies of Meshul and others also show that asymmetric synaptic terminals are enlarged and are the synaptic population which have increased perforated postsynaptic densities (Benes et al., 1985a; Meshul and Casey, 1989; See et al., 1992; Meshul et al., 1994, 1996b), suggesting that striatal glutamatergic

synaptic transmission may, in these terms, be enhanced by antipsychotics (Meshul et al., 1996c). Overall, therefore, evaluation of the net functional effects of antipsychotics upon the circuitry of the striatum — and cortex (Vincent et al., 1991) — must take into account both an altered ratio of synaptic types, as well as probable changes in the properties of constituent synapses. Whilst further studies on the structure–phenotype relationships of the synaptic alterations following antipsychotics are thus necessary, it is clear that the drugs induce a synaptic reorganisation the striatum and lamina VI of frontal cortex which affects both pre- and post-synaptic elements. The correlates of these changes are discussed further in Section 5.

The precise nature of the ultrastructural effects of antipsychotics remains unclear for additional reasons, reflecting incomplete data (e.g., the influence of dose and duration of treatment have not been systematically investigated) and several methodological limitations. Firstly, all experiments have been done in rodents, which may respond neuropathologically in different ways than do humans, or have intrinsic anatomical differences (e.g., in the cellular and synaptic composition of the striatum; Roberts et al., 1996a). There are no non-human primate data. Secondly, only haloperidol has been widely studied, and the possibility that other individual antipsychotics, including the recently introduced agents, have idiosyncratic neuropathological effects cannot be discounted. Thirdly, non-stereological methods have been used in all studies, and the data are therefore prone to error and bias (Oorschot, 1994); on the other hand, making a virtue out of necessity, few of the equivalent studies in schizophrenia have been stereological either (Harrison, 1999).

3.3. Effects of antipsychotics on synaptic markers

The results of the molecular and immunocytochemical studies of synapses (Table 3) are in keeping with the electron microscopy data, in that there are discrete changes in the expression of presynaptic proteins. This supports the occurrence of plasticity which differentially affects synaptic populations in striatum and frontal cortex

Table 3
Animal studies[a] of antipsychotic drug effects on molecular and immunochemical synaptic markers

Study	Drug, dose and duration[b]	Parameters measured	Significant changes in drug-treated animals
Vincent et al., 1994	Haloperidol decanoate 10.5 mg/kg/3 w for 19 w	GABA-positive terminals on pyramidal neurons in medial prefrontal cortex.	Increased size (or GABA content) of terminals; unchanged number
Eastwood et al., 1994	Haloperidol 2 mg/kg/d i.m. for 2 w	Synaptophysin and its mRNA in dorsolateral striatum and frontal cortex	mRNA increased in both areas. Same trend for protein
Eastwood et al., 1995	Haloperidol 2 mg/kg/d i.m. for 2 w[c]	Synaptophysin mRNA in hippocampus	No changes
Kroesen et al., 1995	Haloperidol 1 mg/kg/d or clozapine 20 mg/kg/d i.m. for 10 d	Secretogranin II and chromogranin mRNAs in dorsolateral striatum[d]	Increase in both mRNAs, haloperidol >clozapine
Meshul et al., 1996a	Haloperidol 0.5 mg/kg/d or clozapine 30 mg/kg/d i.m. for 4 w	Glutamate-positive asymmetric striatal synapses, with or without PPD[b]	Both drugs increased glutamate labelling. Only haloperidol did so at synapses with a PPD
Mijnster et al., 1996	Haloperidol decanoate 14 mg/kg i.m., one injection, killed 2 w later	Size and shape of met[5]-enkephalin-positive boutons in dorsal striatum	Boutons enlarged and elongated
Eastwood et al., 1997	Haloperidol decanoate 2 mg/kg/3 w i.m. for 16 w	Synaptophysin, its mRNA, and GAP-43 mRNA in dorsolateral striatum, frontal cortex and hippocampus	Synaptophysin results as in Eastwood et al. (1994, 1995) above. No changes in GAP-43 mRNA
Marin and Tolosa, 1997	Haloperidol, 1 mg/kg/d i.m. for 3 w, killed 4 d later	Synaptophysin in striatal homogenates	Increased 88%
Nakahara et al., 1998	Haloperidol decanoate 25 mg/kg i.m., one injection, killed 4 w later	Synaptobrevin II, synaptotagmin I and IV, syntaxin IA, SNAP-25, rab 3a and synaptophysin mRNAs in striatum, frontal cortex and midbrain	Synaptobrevin, synaptotagmins, syntaxin 1A and rab3a mRNAs decreased in n.accumbens. No other changes
Eastwood and Harrison (unpublished)	Haloperidol 1 mg/kg/d, chlorpromazine 15 mg/kg/d, clozapine 2 5mg/kg/d, risperidone 0.5 mg/kg/d, olanzapine 5 mg/kg/d i.m. for 2 w	Synaptophysin mRNA in dorsolateral striatum, frontal cortex and hippocampus	Increased in striatum by chlorpromazine, with trend for haloperidol

[a] All studies were carried out in rats.
[b] d: days; w: weeks; m: months. i.m.: intramuscular injection; PPD: perforated postsynaptic density.
[c] Same animals as in Eastwood et al. (1994).
[d] Other nuclei also measured.

(Eastwood et al., 1994, 1997; Kroesen et al., 1995; Marin and Tolosa, 1997; Nakahara et al., 1998).

4. Human studies

4.1. Neuropathological findings in antipsychotic-treated patients

The most valuable human study of the neuropathological effects of antipsychotics is that by Jellinger (1977). His chapter also includes a summary of the case reports and series published prior to that time. Jellinger investigated 28 patients treated chronically with antipsychotics, most of whom had a diagnosis of schizophrenia. Fourteen had significant dyskinesia. The 28 cases were compared with a series of unmedicated schizophrenics, and a series of neurologically normal, age-matched controls. Treated subjects with and without dyskinesia were also compared. Thus, an attempt was made to control for the confounding variables of age, psychosis, and dyskinesia. Unfortunately, the data are not presented clearly, and the study was only semi-quantitative.

Alterations were limited largely to the rostral part of the caudate nucleus. The most common changes were swollen large neurons, glial satellitosis, and sometimes a more generalised gliosis, found in 46% of the antipsychotic-treated group compared to 4% of the untreated schizophrenics and 2% of the controls. The observations concerning large neurons are of potential interest, since they are cholinergic interneurons, noted in other studies to be affected by antipsychotics (Mahadik et al., 1988; Jeste et al., 1992; Eastwood et al., 1994) and in medicated schizophrenics (Holt et al., 1994; see also Miller and Chouinard, 1993).

Antipsychotic-treated cases with dyskinesia had a slightly greater incidence of pathology (57%) than those without (37.5%). The occurrence of pathological changes did not relate to diagnosis or age. No consistent pathological effects of antipsychotics were found in other regions, although the extent of the search is not stated. Electron microscopy studies of the striatum were performed in two of the dyskinetic patients: enlarged axons were found, together with increased numbers of mitochondria and abnormal organelles.

The lack of neuropathological abnormalities outside the caudate nucleus is in contrast to the other significant post-mortem series, which comprised 28 patients dying with dyskinesia, 21 of whom had been treated long-term with antipsychotics (Christensen et al., 1970). (The paper does not allow the latter subgroup to be analysed separately.) In the dyskinetic group, a higher incidence of gliosis (89%) and neuronal degeneration (89%) in the substantia nigra and brainstem was reported than in controls (25% and 14%, respectively). However, the control group was poorly matched, and in the light of other negative data (see Jellinger, 1977), the robustness and interpretation of these nigral and brainstem changes is uncertain.

Neither of the above two series are directly comparable with the more molecular and quantitative approaches being taken in contemporary neuropathological studies of schizophrenia. As such, it is difficult to interpret the results, and their findings must be considered together with the results of the alternative approaches to the issue of medication effects (Section 2). Nevertheless, it is noteworthy that the human findings are anatomically congruent with those in rats, in that morphological changes are greatest in — and arguably have only been well demonstrated in — the basal ganglia.

4.2. Do antipsychotics promote Alzheimer's disease?

The suggestion that antipsychotics can cause, or at least predispose to, Alzheimer's disease has arisen for two reasons. Firstly, it has sometimes been stated that people with schizophrenia have an increased risk of Alzheimer's disease. [The origins of the claim lie in two German papers of the 1930s (Corsellis, 1962), and it was reiterated in the report from which the infamous "schizophrenia has been the graveyard of neuropathologists" quote is taken (Plum, 1972).] Secondly, Wisniewski et al. (1994) reported a higher incidence of neurofibrillary tangles in schizophrenics who had been treated with antipsychotics (and who died between 1954 and 1990) than in those who had not received the drugs because they died before 1952 (74% vs 36%). They also found hippocampal neuronal density to be decreased by ∼25% in the medicated group.

In fact, there is now overwhelming evidence that Alzheimer's disease is not more common in schizophrenia, even in subjects with unequivocal dementia (see Harrison, 1997, 1999). This negative conclusion was confirmed in a meta-analysis which found an overall odds ratio of 0.86 (95% confidence interval, 0.65–1.15) for the prevalence of Alzheimer's disease in schizophrenia (Baldessarini et al., 1997) and corroborated in four subsequent studies (Arnold et al., 1998; Murphy et al., 1998; Purohit et al., 1998; Jellinger and Gabriel, 1999). Interpretation of the findings of Wisniewski et al. (1994) is difficult anyway, given the doubtful comparability of the two cohorts (e.g., with regard to diagnostic criteria, effect of differing storage times) and the statistical analysis used (Baldessarini et al., 1997).

Parenthetically, in vitro data reveal that some phenothiazines inhibit the aggregation of tau (Wischik et al., 1996) and the formation (Higaki et al., 1997) and neurotoxicity (Ueda et al., 1997) of β-amyloid — suggesting that antipsychotics might, if anything, be protective against Alzheimer-type neuropathology.

4.3. Which neuropathological findings in schizophrenia are likely to be confounded by antipsychotic treatment?

The data reviewed above indicate that neuropathological studies of schizophrenia may be affected by antipsychotic treatment. Investigations of the caudate nucleus are especially vulnerable given the range of reported effects on its synapses, neurons and perhaps glia (Tables 1–3). However,

even in this region, recent data suggest a qualitatively different pattern of synaptic pathology associated with schizophrenia than that due to antipsychotics implying that, with appropriate caution, the two factors can be disentangled (Roberts et al., 1996b; Uranova et al., 1996; Kung et al., 1998; Kung and Roberts, 1999). Studies of synapses in the frontal cortex, at least in lamina VI, must also be interpreted carefully in the light of the ultrastructural and synaptic protein findings in antipsychotic-treated rats (Tables 2 and 3). There is no evidence that antipsychotics affect cortical neurons (Table 1) or produce neuropathological effects in the hippocampus (Tables 2 and 3) — albeit the data are limited in the latter region — and hence are unlikely to be major confounders of the morphometric and cytoarchitectural findings in schizophrenia reported therein. The only caveat regarding hippocampal studies is the report of haloperidol-induced granule cell proliferation (Dawirs et al., 1998) which hypothetically might confound dentate gyrus measurements.

5. Causes and correlates of antipsychotic-induced neuropathological effects

The range of ultrastructural parameters seen to be altered in response to antipsychotic drugs are together indicative of a drug-induced synaptic plasticity (Eastwood et al., 1997). For example, perforated postsynaptic densities are a sign of a newly formed or forming synapse, and the higher proportion of synapses with perforated postsynaptic densities after antipsychotics thus likely reflects increased synaptic formation or turnover (Genisman et al., 1989). Similarly, changes in the size and density of dendritic spines occur in response to afferent stimulation and many other stimuli (Calverley and Jones, 1990). The question arises as to the processes leading to such antipsychotic-induced synaptic plasticity, as well as its likely functional consequences.

One clue as to the clinical correlates of synaptic plasticity is provided by the anatomical distribution of the alterations. The antipsychotic action of antipsychotic drugs is generally attributed to blockade of mesolimbic D2 receptor-mediated dopamine transmission in the nucleus accumbens or cortex, whereas extra-pyramidal side-effects (EPS), including tardive dyskinesia arise from D2 receptor blockade, and perhaps an accompanying dopaminergic supersensitivity, in the nigrostriatal pathway (see Feldman et al., 1997; Lidow et al., 1998). Nearly all the ultrastructural changes seen after antipsychotic treatment have been reported in the latter region, notably the caudate nucleus, with the nucleus accumbens unaffected (Table 2). As such, it may be argued that the neuropathological effects of the drugs are likely to relate more to their propensity to cause tardive dyskinesia, or indeed to some other mechanism specific to the dorsolateral striatal circuitry, rather than to their therapeutic efficacy or any neurochemical correlate thereof. The fact that clozapine produces lesser and differing ultrastructural changes (Vincent et al., 1991; Meshul et al., 1992, 1996a) and no striatal volume increase (Chakos et al., 1995) supports this view, in that it parallels the absence of tardive dyskinesia and other EPS associated with the drug. Furthermore, some studies have shown that antipsychotic-treated subjects, whether rats or humans, exhibiting dyskinesias and other motor disturbances have greater and/or differential ultrastructural alterations than those who do not (Jellinger, 1977; See et al., 1992; Roberts et al., 1995; Meshul et al., 1996b). However, the data as a whole are insufficient for, and in places inconsistent with, a straightforward clinico-pathological relationship of this kind. For example, some structural changes induced by antipsychotics do not differ between those with and without dyskinesias (Roberts et al., 1995; Meshul et al., 1996b; Kelley et al., 1997; Chakos et al., 1998), nor with dopaminergic supersensitivity (Marin and Tolosa, 1997). In any event, the pathophysiology of EPS is poorly understood (Seeman, 1988; Casey, 1995), and the equivalence of abnormal movements in rats with tardive dyskinesia in patients is uncertain (Tamminga et al., 1990; Waddington, 1990). As such, elucidating the clinical correlates of the ultrastructural effects of antipsychotic drugs will require considerable further investigation.

The pharmacological and cellular mechanisms underlying the neuropathological effects of antipsychotics are mediated at least in part by dopa-

mine D1 and D2 receptors (Meshul et al., 1992) and NMDA receptors (Meshul et al., 1994), and may be counteracted by ganglioside-mediated prevention of excitotoxicity (Meshul et al., 1995), but the downstream sequence of events, and the contribution of other receptors and intracellular pathways, are otherwise unknown.

6. Neuropathological effects of other treatments

6.1. Electroconvulsive therapy

A comprehensive recent review concluded that ECT has no demonstrable structural effects (Devenand et al., 1994). Whilst reassuring, there are minor caveats. The presence of subtle changes in neurons and synapses following ECT akin to those reported in schizophrenia has not been investigated in human brain; in rats administered electroconvulsive shocks, alterations in synaptic proteins (Jorgensen and Bolwig, 1979) and enhanced expression of the astrocytic marker glial fibrillary acidic protein (GFAP; Orzi et al., 1990; Steward, 1994) and of the dendritic microtubule-associated protein MAP-2 (Pei et al., 1998) have been reported, as well as hippocampal neurotoxicity (Enns et al., 1996). Though the applicability of the animal experiments to the clinical situation is questionable, since a higher stimulus intensity is used and only short-term effects have been measured (see Devenand et al., 1994), it would be prudent to bear the data in mind when studying the brain of a person who had received ECT in the weeks prior to death.

6.2. Lithium

Case reports (Schneider and Mirra, 1994) and studies in monkeys (Akai et al., 1977) show that fatal lithium overdose is associated with a variety of findings in keeping with an acute neurotoxicity. Whether long-term treatment with lithium at therapeutic levels produces neuropathological effects is much less clear, since there have been no such studies of humans or monkeys. In rats, lithium administered for 30 weeks at serum levels of 0.5–0.8 mmol/l (with or without concurrent haloperi-

dol at 1 mg/kg/day) did not affect the number, density or size of cortical neurons assessed stereologically (Licht et al., 1994). A 30–40% elevation of GFAP was reported in the caudate nucleus and hippocampus of rats administered lithium (0.6–1.2 mmol/l) for 4 weeks (Rocha and Rodnight, 1994), augmented recently by direct evidence for hippocampal astrocytic gliosis after the same treatment (Rocha et al., 1998).

6.3. Antidepressants

Experimentally, antidepressants have been reported to have subtle histological effects (Smialowska et al., 1988; Nakamura, 1990; Kitayama et al., 1997) and measurements in human cerebrospinal fluid suggest that they may interfere with β-amyloid precursor protein metabolism (Clarke et al., 1993). There are no relevant neuropathological data.

6.4. Historical treatments

Amongst the subjects included in post-mortem studies are elderly patients who were subjected to insulin coma therapy or leucotomy. Although the impact of these interventions is likely to be less than that of antipsychotics, if only because a smaller proportion of the subjects have received them, they are still potential neuropathological confounders (Roizin, 1972; Pakkenberg, 1989).

7. Conclusions

The best documented histological effects of antipsychotic drugs are in the striatum, where neuronal and synaptic structure has been shown to be affected in rats, with circumstantial evidence for a comparable process in humans. There is also reasonable evidence, in rats, for a subtle synaptic reorganisation in deep laminae of the frontal cortex. Caution should therefore be exercised when interpreting neuropathological findings affecting similar indices in these areas in schizophrenia; this applies not only to ultrastructural and morphometric analyses, but also to measurements of gene products used as proxies. There is little or no

indication that antipsychotic treatment produces morphological changes in the hippocampus, wherein many of the recent positive findings in schizophrenia have been reported. Neither is there any good evidence that antipsychotics promote Alzheimer's disease neuropathology in general nor neurofibrillary degeneration in particular.

The potential neuropathological influence of antipsychotics vis-á-vis schizophrenia must continue to be taken into account, especially as new techniques are introduced, novel parameters measured, and different brain areas studied. It will be worth examining whether the drugs have lateralised histological effects, given the evidence for asymmetrical alterations seen in some MRI studies of the basal ganglia in medicated subjects (Elkashef et al., 1994; Gur et al., 1998). As patients treated with atypical antipsychotics begin to be included in post-mortem series, this class of agent will need more detailed consideration as well. Together, a combination of the approaches listed in the Introduction will ensure that the neuropathological effects of antipsychotics, and of other interventions, can continue to be disentangled from those of schizophrenia itself.

Acknowledgements

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