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Effects of typical and atypical antipsychotics on prepulse inhibition in schizophrenia: a critical evaluation of current evidence and directions for future research

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Abstract Prepulse inhibition (PPI) of the startle response refers to an attenuation in response to a strong stimulus (pulse) if this is preceded shortly by a weak non-startling stimulus (prepulse). PPI provides a simple operational measure of sensorimotor gating, serving to prevent the interruption of ongoing perceptual and early sensory analysis. In accord with postulated deficits in early stages of information processing, there is ample evidence that PPI is disrupted in individuals with schizophrenia. PPI in animals is thought to represent a well-validated model for evaluating potential new treatments for schizophrenia. Currently, available data on the differential effects of typical and atypical antipsychotics suggest that atypical antipsychotics, in particular clozapine and risperidone, may be more effective than typical antipsychotics in improving PPI deficits in schizophrenia. However, studies have so far used small samples and/or between-subjects designs, and not examined the effects of other concomitant medications that may also influence PPI. The directions are identified for further applications of this model using within-subjects longitudinal designs and reasonable sample sizes to establish superiority of particular atypical antipsychotics over typical antipsychotics in improving PPI in schizophrenic populations.

Keywords Startle response · Prepulse inhibition · Schizophrenia · Typical and atypical antipsychotics

Introduction

The simple startle reflexive response is known to show several forms of plasticity, both in animals and human beings. One form of startle plasticity is known as prepulse inhibition (PPI). PPI refers to a reliable reduction in the amplitude of the response to a strong sensory stimulus, the pulse, if this is preceded by 30–500 ms by a weak stimulus, the prepulse (Graham 1975). This weak prestimulus, although not strong enough to elicit a measurable startle response itself, evokes inhibitory mechanisms, which presumably gate further stimulation until the processing of the prepulse has been achieved. This results in disrupted processing and reduced impact of the pulse, and hence the PPI effect. PPI thus serves the function of avoiding behavioural interference that might otherwise arise from the simultaneous processing of discrete stimuli. Deficits in the ability to avoid such interference are thought to lead to sensory over-stimulation and behavioural confusion (Braff 1993). The most commonly used paradigms to demonstrate PPI in a laboratory setting have employed acoustic stimuli both as the pulse (a strong noise-burst) and the prepulse (a weak noise). In normal human subjects, the effect is maximally noticed with a stimulus-onset asynchrony (SOA, the time from prepulse onset to pulse onset) of 120 ms, with shorter and longer SOAs producing relatively less PPI.

Consistent with Graham's (1975) suggestion that PPI may provide a sensitive measure of sensorimotor gating deficits in schizophrenia and thus advance the understanding of the well-documented deficiency of schizophrenics to efficiently process rapidly presented sensory information, Braff and colleagues (1978) demonstrated impaired PPI in schizophrenic patients. There has been a continued interest in PPI since then and several subsequent studies have demonstrated impaired PPI in schizophrenic populations (Braff and Geyer 1990; Braff et al. 1992; Grillon et al. 1992; Kumari et al. 1999). The conceptualization that impaired inhibitory processes underlying deficient PPI leads to cognitive fragmentation in schizophrenia (McGhie and Chapman 1961) is supported

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by a number of empirical observations. Impaired PPI predicts poor responses on the Ego Impairment Index—human experience scale, a measure of thought disorder (Perry and Braff 1994; Perry et al. 1999) and correlates positively with a number of other cognitive deficits, for example, poor performance on the Wisconsin Card Sort Test (Butler et al. 1991), and distractibility (Karper et al. 1996) in schizophrenic patients. PPI has shown a modestly positive relationship with both positive and negative symptoms of schizophrenia in some studies (Braff et al. 1999; Weike et al. 2000), but not in others (Perry and Braff 1994; Kumari et al. 1999). As proposed by Braff and colleagues (1999), PPI deficits may correlate more strongly with cognitive abnormalities and thought disorder than with schizophrenic symptoms.

Antipsychotic drugs and PPI

PPI in animals is thought to represent one of the most established models to study information processing deficits and their normalisation by pharmacological treatments in schizophrenia (for excellent reviews of this topic, see Swerdlow et al. 1992, 1994, 2000; Swerdlow and Geyer 1998). Briefly, atypical antipsychotics appear equally effective as typical antipsychotics in reversing dopamine (DA)- and social isolation-induced PPI deficits, but superior in reversing serotonin (5-HT) and *N*-methyl-D-aspartate (NMDA) antagonist-induced disruptions of PPI. Schizophrenia is believed to involve disturbances of several neurotransmitters (Busatto and Kerwin 1997; Carlsson 1998). Newer atypical antipsychotics act on a wider range of neuroreceptors than typical antipsychotics (Arnt and Skarsfeldt 1998; Moller 2000) and appear to have beneficial effects on a range of cognitive variables and positive as well as negative symptoms (Sharma 1999). This article examines whether they are also more effective than typical antipsychotics in normalizing PPI in schizophrenia. The effects in normal subjects are also examined with a view to help us understand antipsychotic drug effects on PPI in the absence of any psychopathology.

Typical antipsychotics

Our group (Kumari et al. 1998) has investigated the effects of 2 mg and 5 mg haloperidol, as well as the effects of 5-mg *D*-amphetamine administration on PPI at 30, 60, and 120-ms SOAs in normal subjects. Haloperidol disrupted PPI at all SOAs, though this effect was restricted to the high dose (5 mg; expected to produce over 75% DA D2 receptor blockade; Nordstrom et al. 1992) and to smoking subjects only. Disruption of PPI with 5 mg *D*-amphetamine was also seen in smoking subjects only. Another study (Abduljawad et al. 1998) found that 3 mg oral haloperidol disrupted PPI in normal subjects at 120-ms SOA (no other SOA examined), though it was effective in antagonising the PPI-disruptive effect of the

DA-D2-like agonist bromocriptine (1.25 mg). Taken together, the data appear to suggest that both hyper-dopaminergic (i.e. induced by the administration of DA agonists) as well as hypo-dopaminergic states (i.e. induced by high doses of DA antagonists) reduce PPI in healthy subjects.

The findings noted above in healthy subjects for haloperidol might also suggest that PPI deficits seen in schizophrenic patients given typical antipsychotics resulted from the typical drug therapy, rather than because of the illness itself. Previous studies (Braff et al. 1978, 1992; Grillon et al. 1992; Perry and Braff 1994) observed PPI deficits in schizophrenic patients, the majority of whom were (presumably) on typical antipsychotic medication. There are, however, several lines of evidence that suggest that typical antipsychotics were not responsible for PPI deficits in schizophrenic patients seen in previous studies. First, the effects seen in normal subjects with one single acute dose of drug are unlikely to reflect those seen with chronic use in schizophrenic populations. In rats, DA manipulations involving repeated exposures are known to produce different effects on PPI from those seen with single administration (Taylor et al. 1995; Martinez et al. 2000). Further, unless deficits are first induced by some pharmacological or experimental means, antipsychotic efficacy, which should take the form of deficit correction, cannot be determined in normal subjects. Second, PPI deficits are found in drug-free patients with a clinical diagnosis of schizophrenia (Weike et al. 2000), and also extend to schizophrenia-related populations, for example to normal volunteers scoring high on the psychometric measures of psychosis-proneness (Simons and Giardina 1992; Kumari et al. 1997), or patients with schizotypal personality disorder (Cadenhead et al. 1993; only 2 of 16 patients receiving low doses of antipsychotics at the time of testing). More recently, unaffected relatives of patients with schizophrenia have also been found to exhibit reduced PPI relative to healthy people (Cadenhead et al. 2000).

The data from unmedicated populations suggest that typical antipsychotics are unlikely to cause PPI deficits in schizophrenic patients, but do they improve PPI? It seems that PPI deficits seen in previous studies in patients treated with typical antipsychotics reflected a partial rather than a full normalisation of underlying deficits in postulated PPI circuit with inputs from dopaminergic as well as from non-dopaminergic systems (Swerdlow et al. 1992). These early findings may also reflect a dose–response relationship between improvement in PPI and typical antipsychotics. Patients in some previous studies were on considerably higher doses as reported in chlorpromazine (cpz) equivalents (Braff et al. 1992, mean daily dose = 2245.2 ± 262.9 mg; Grillon et al. 1992, mean daily dose = 1640 ± 499 mg) than those reported in a recent study (Kumari et al. 2000, mean daily drug dose = 432.27 ± 345.13 mg), which showed normal range PPI at 120-ms SOA in patients given typical antipsychotics.

Atypical antipsychotics

Several research groups, including our own, following the observations regarding differential effects of typical and atypical antipsychotics in some PPI models in experimental animals, have focused on the differential effects of typical and atypical antipsychotics on passive PPI (i.e. subjects not instructed to pay any attention to the prepulses; more likely to parallel paradigms employed in animal studies) in schizophrenic patients. We (Kumari et al. 2000) observed greater PPI in patients given atypical antipsychotics than those given typical antipsychotics. However, the superiority of atypical antipsychotics ($n=29$) in our study was limited to short–medium SOAs, i.e. 30 ms and 60 ms; at 120-ms SOA, patients on typical antipsychotics ($n=9$) also showed normal PPI (controls $n=20$). There are other recently published studies (Ford et al. 1999; Weike et al. 2000) that included patients medicated with typical and atypical antipsychotics (i.e. mixed samples) which found no significant difference between patients and healthy subjects. Weike and colleagues (2000) reported reduced PPI in unmedicated ($n=5$) patients but normal PPI in patients treated effectively with a range of antipsychotics (typical $n=11$, atypical $n=9$) relative to 12 matched controls. They, however, did not report data separately for patients treated with typical and atypical antipsychotics. In general, there are early indications that atypical antipsychotics may be more effective in improving PPI than typical antipsychotics in schizophrenia. However, various atypical antipsychotics are known to differ in their pharmacological and clinical profiles (Arnt and Skarsfeldt 1998; Moller 2000; Remington and Kapur 2000). It is therefore important to consider their effects separately.

So far only clozapine and risperidone have been studied in this respect, and they both appear to be superior to typical antipsychotics. We (Kumari et al. 1999) examined passive PPI in two groups of schizophrenic patients: (i) on clozapine ($n=11$), and (ii) on a range of typical antipsychotics ($n=9$) compared with a group of healthy subjects ($n=13$). Patients on typical antipsychotics were found to show less PPI with 30-ms and 60-ms prepulse trials than healthy subjects. Clozapine-treated patients showed normal levels of PPI. Extending this work (Kumari et al. 1999), we (Kumari et al. 2002) further examined passive PPI in risperidone-treated patients ($n=10$) and found that they, too, did not differ from control subjects, whereas an extended sample of typically treated patients showed reduced PPI at short–medium SOAs ($n=20$, including 9 patients reported in Kumari et al. 1999).

The superiority of clozapine over typical antipsychotics in improving PPI has been attributed to its pharmacological (5-HT) effects on prefrontal regions of the brain or to its effects on a broader range of neuroreceptors than typical antipsychotics (Kumari et al. 1999). Similar mechanisms may be conceived for the effects of risperidone (Honey et al. 1999). However, other mechanisms may also be involved that have not been previously considered. For example, the effects of atypical drugs may

involve a change in concomitant medication with substitution of atypical antipsychotics for typical antipsychotics. Anticholinergic drugs are invariably used to counteract extrapyramidal symptoms induced by antipsychotic medication, especially with typical antipsychotics, in schizophrenic patients (Van Putten and Marder 1987). It has recently been found (Kumari et al. 2001a) that procyclidine, the most commonly prescribed anticholinergic drug in the UK to counteract extrapyramidal symptoms in patients with schizophrenia, also disrupts PPI in a dose-dependent manner in normal subjects. This raises a further concern. Clozapine is a potent anticholinergic (Arnt and Skarsfeldt 1998; Moller 2000) yet it appears to improve PPI more than typical antipsychotics. Given that in animal studies both hyper- and hypocholinergia appear to disrupt PPI (review, Swerdlow et al. 1992), it would appear that there is a response range, and clozapine-treated patients remained within this range because clozapine also has procholinergic effects (Davydov and Botts 2000). Another puzzling observation is that treatment with clozapine reduces ad lib cigarette smoking in patients (Procyshyn et al. 2001). Given that cigarette smoking too improves PPI in normal (Kumari et al. 1996) and schizophrenic populations (Kumari et al. 2001b), the mechanisms for the effects of clozapine seem rather complex and may not be applicable to other atypical antipsychotics.

Critical evaluation of current evidence

PPI with its high test–retest reliability in normal (Cadenhead et al. 1999) and schizophrenic populations (Ludewig et al. 2002) provides a unique opportunity to examine the differential effects of various antipsychotic drug treatments, as well as predictors and consequences of responsiveness to various old and newer antipsychotics in schizophrenia. Previously published reports of deficient PPI in unmedicated patients, coupled with those showing (a) deficient PPI in patients (presumably) given typical antipsychotics and (b) an improvement with typical antipsychotics in unmedicated patients, indicate that typical antipsychotics improve PPI deficits, but may not fully normalise them. Atypical antipsychotics, in particular clozapine and risperidone, have shown promise of relatively better improvement in PPI. However, the data published so far have come from small sample studies, between-subjects designs with non-random allocation of patients to receive typical or atypical drugs. Such data do not allow a definite interpretation as to whether normal-range PPI in patients treated with some atypical drugs reflected real improvements in PPI or some uncontrolled clinical bias towards less severe patients receiving atypical drugs. Admittedly this is unlikely to be the case for clozapine, which was only prescribed to patients [in the UK at the time the study by Kumari et al. (1999) was carried out] if they had failed to show adequate responses to typical and at least two other atypical antipsychotics.

Directions for future research

1. Further studies should investigate the effects of typical and various atypical antipsychotics in schizophrenia in within-subjects longitudinal designs with random allocation of drug treatments and careful attention to other concomitant medications. Further, given the differential effects of typical and atypical drugs on short-medium SOAs seen in between-subjects designs, future studies should use experimental paradigms with a broad range of SOAs.
2. There is some evidence that PPI abnormalities are related to other cognitive abnormalities, but there is a paucity of research in this area. Given that cognitive improvement is a strong predictor of functional outcome in schizophrenia (Green 1996), concurrent measurements of multiple clinical, cognitive and functional outcome variables need to be included in future investigations of changes in PPI with atypical antipsychotics for this line of enquiry to meaningfully relate to the clinical neuroscience.
3. A further extension of the proposed approach is required to include the examination of low doses of typical and atypical antipsychotics in unaffected relatives of schizophrenic patients who are non-symptomatic but exhibit (presumably trait-linked) reduced PPI. The improvements in PPI with antipsychotic medication in schizophrenic patients suggest PPI deficits to represent a 'state' variable (Swerdlow et al. 2000). However, the observations of reduced PPI in non-psychotic patients with schizotypal personality disorder (Cadenhead et al. 1993) and in non-affected first-degree relatives of schizophrenia patients (Cadenhead et al. 1999) indicate them to represent a "trait-like" deficit. As speculated by Swerdlow et al. (2000), separate anatomical substrates may be responsible for reversible "state" and fixed "trait"-linked PPI deficits in this disorder, of which "state"-linked neural substrates may respond differently to typical and atypical antipsychotics.
4. It would be informative for future studies to include additional measures such as D2-receptor occupancy (Oades et al. 2000) in order to fully elucidate the relationship between typical antipsychotic drug doses and PPI. Although, in general, studies have not found a significant correlation between PPI and cpz levels suggesting that the dose-response effect, if any, is likely to be small, it is still worth following up.
5. The evidence in rodents points to a genetic control of PPI (Paylor and Crawley 1997). Strong interactions have been found between rat strain and drug administration to affect PPI (Swerdlow et al. 2000). Further studies could perhaps explore differential effects of typical and atypical antipsychotic drugs in familial versus non-familial schizophrenia.

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