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Research Overview

Screening of Antipsychotic Drugs in Animal Models

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Strategy, Management and Health Policy				
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ABSTRACT Behavioral models of antipsychotic drug (APD) action in the rat are widely used for the screening and developing APDs. Valid models are not only required to be selective and specific for APDs, but also to be able to dissociate between typical and atypical APDs. In recent years, newer models have been developed that are claimed to model processes impaired in schizophrenic patients. However, these models depend on previous administration of propsychotic drugs for revealing the effects of APDs, raising the possibility that the "model" of APD action is not the specific behavior assessed but the administration of the propsychotic drug. A valid behavioral model of APD action should posses the following characteristics: 1) The behavior assessed in the model has relevance to the clinical condition; 2) The behavioral paradigm used to index the action of APDs can be used in rats and humans. 3) The model is selective and specific to APDs differing in their in vitro and in vivo pharmacology. 4) The model can dissociate between typical and atypical APDs. and 5) The model does not require previous pharmacological manipulations to manifest the behavioral index of antipsychotic activity. In this overview, data are summarized showing that the latent inhibition (LI) model of APD action, which measures a cognitive process known to be impaired in schizophrenia, namely, the ability to ignore stimuli that had been inconsequential in the past, fulfills all of the above criteria. The utility of the LI model can be further extended when it is combined with the forced swim test (FST) model, which is sensitive to the antidepressant-like activity of the atypical APDs, such that the combined LI-FST model can dissociate between typical APDs, atypical APDs, and antidepressants. Finally, the use of the LI model alone or in combination with FST in rats that sustain lesions or other physiological manipulations (e.g., stimulation) to specific brain regions may provide clues as to the relationship between the effects of these drugs and the site of brain damage, and possibly reveal differential effects of typical and atypical APDs, depending on the site of the damage. Drug Dev. Res. 50:235–249, 2000.

Key words: antipsychotic drugs; animal model; latent inhibition; forced swim test; schizophrenia

INTRODUCTION

The common feature of all currently used antipsychotic drugs (APDs) is the blockade of the dopamine (DA) D2 receptor subfamily. Although this action is apparently responsible for their antipsychotic activity, it also induces extrapyramidal side effects (EPS). Based on the clinical features of clozapine, which produces less or no EPS without losing antipsychotic efficacy, much effort has been invested for more than a decade in developing additional APDs that fulfill these criteria. As a result, APDs are currently divided into two groups—typical and atypical. There are several criteria for this distinction, extensively reviewed elsewhere [Brunello et al., 1995; Kinon and Lieberman, 1996; Arnt and Skarsfeldt, 1998]. The most commonly accepted criteria for atypicality are a reduced capacity to cause EPS (resulting in a large difference between the dosages that control psychosis and induce EPS), superior therapeutic efficacy for negative symptoms/treatment-resistant schizophrenic symptoms, and a reduced capacity to induce catalepsy in rodents.

In addition, atypical APDs can be characterized by limbic versus nigrostriatal DA selectivity, and most have

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a broad receptor profile, including effects on DA receptors (D1, D2, D3, D4, D5), serotonin receptors (5-HT_{2A}, 5-HT_{2C}), α1-adrenoreceptors, muscarinic receptors, and histamine receptors. It is largely accepted that although D2 occupancy is required for antipsychotic activity, mixed DA2–5-HT_2 antagonism is the common feature of atypical APDs that is responsible for the improved antipsychotic efficacy/EPS ratio of these compounds [e.g., Meltzer, 1989; Leysen et al., 1993; Brunello et al., 1995; Schotte et al., 1996; Arnt and Skarsfeldt, 1998]. However, the distinction between typical and atypical APDs is far from clear-cut, because atypical compounds differ markedly in their receptor affinity patterns and their relative affinities for the same receptor sites, and some typical compounds possess a wide receptor profile. The problem is compounded by the ongoing debate regarding the validity of the positive–negative symptom dichotomy in schizophrenia, the definition of negative symptoms (primary or deficit versus secondary), and the relative efficacy of typical versus atypical APDs in the treatment of negative symptoms [e.g., Carpenter et al., 1988; Kay and Singh, 1989; Tandon et al., 1990; Kane, 1995; Tandon, 1995; King, 1998].

Behavioral models of antipsychotic activity in the rat are widely used for screening and developing APDs, as well as for elucidating their mechanism of action. Currently, valid models are not only required to be selective and specific for APDs, but also to be able to dissociate between typical and atypical APDs.

One feature that distinguishes between the different models that is commonly disregarded but is of central importance is their dependence on pharmacological means for revealing APD effects. Thus, two major classes of models can be delineated: those that use APDs in combination with other (usually "propsychotic," but see below) drugs (pharmacological or drug–drug models), and those that test the effects of APDs given on their own (nonpharmacological models). The former category includes the classic model of the inhibition of hyperactivity and stereotypy induced by DA agonists/releasers, e.g., apomorphine and amphetamine, as well as a more recent version that uses the noncompetitive *N*-methyl-D-aspartate (NMDA) antagonists, phencyclidine (PCP) or dizocilpine (MK-801). These models have allowed a differentiation between typical and atypical APDs, e.g., the former inhibit hyperactivity and stereotypy induced by DA drugs and induce catalepsy at similar dose levels, whereas the latter selectively inhibit hyperactivity without affecting stereotypy and catalepsy; however, also in this model, atypical compounds exhibit different behavioral profiles that apparently depend on their specific receptor profiles [Arnt and Skarsfeldt, 1998].

In addition to these classic models, newer models have been developed that are claimed to model processes impaired in schizophrenic patients, and have the capacity to dissociate between typical and atypical APDs, notably, apomorphine-, PCP-, or MK-801-induced deficits in prepulse inhibition (PPI) [Hoffman et al., 1993; Swerdlow and Geyer, 1993; Bakshi et al., 1994; Swerdlow et al., 1994; Bakshi and Geyer 1995], and PCP- or MK-801-induced deficits in social interactions [Corbett et al., 1993, 1995; Sams-Dodd 1996, 1997]. Although the latter models have an obvious advantage of clinical relevance and the appeal of face and even construct validity, which may account for their growing popularity, their dependence on propsychotic drug administration has two related drawbacks: First, such models are likely to reveal only antipsychotic action that is mediated via neurotransmitter systems affected by the challenge drug. Second, it raises the possibility that the "model" of APD action is not the specific behavior assessed but the administration of the propsychotic drug. Although this by itself is legitimate, it should alert us to the questionable germaneness of the behavioral aspect of the models.

For example, in the PPI model, reversal of apomorphine-induced disruption does not dissociate between typical and atypical APDs, but reversal of NMDA antagonist-induced disruption apparently does [although conflicting results have been reported; Johansson et al., 1994; Hoffman et al., 1993; Varty and Higgins, 1995], suggesting that behavioral PCP effects in general rather than disrupted PPI in particular are selectively sensitive to atypical APDs. The latter is supported by the findings that two additional PCP-based behavioral models, namely, social interaction and forced swim test (FST) [Noda et al., 1995] dissociate between typical and atypical APDs. One way to improve such models would be to show that the behavioral deficit alleviated by atypical APDs is itself selective and specific for one class of propsychotic drugs. This might be the case for the social interaction model in the rat, in which PCP but not amphetamine produces social isolation [Corbett et al., 1995; Sams-Dodd, 1996; although amphetamine was shown to produce social isolation, reversible by clozapine, in Java monkeys, Ellenbroek et al., 1996].

Finally, we will comment on an additional aspect of the "clinically relevant" drug–drug behavioral models that has not received attention. Because these models aspire to posses not only predictive validity (e.g., the capacity to predict drug effects), but also construct validity (e.g., commonality of underlying mechanisms in the model and the modeled disorder) [Willner, 1991], the deficit-inducing drugs must be propsychotic in humans. Apomorphine does not fulfill this criterion because, as opposed to amphetamine and PCP, this drug does not produce psychotic symptoms in humans. It is therefore surprising that the most widely used model, PPI disruption, has been based for years on apomorphine administration, while having

difficulties in showing disruption by amphetamine (which is obtained only with high, stereotypy-producing doses).

Purely behavioral models of APD action include those assessing the unconditioned effects of APDs on behavior, such as catalepsy or vacuous chewing movements, as well as those assessing APD effects on a wide range of conditioned behaviors such as avoidance, operant responding, water maze, delayed nonmatch to position, learned helplessness, conditioned fear responses, etc. [e.g., Iversen et al., 1980; Janssen et al., 1988; Glenthoj and Hemmingsen, 1989; Moore et al., 1992; Ogren et al., 1984, 1994; Wiley et al., 1993; Didriksen, 1995; Sanger and Perrault, 1995; Seeger et al., 1995; Skarsfeldt, 1996]. Although such models are free of the problems associated with the prerequisite of previous drug administration noted above, their disadvantage lies in the lack of obvious relevance to the clinical condition [Worms et al., 1983; Arnt and Skarsfeldt, 1998], or at least, the lack of sufficiently rigorous theoretical attempts to establish such a relevance. Indeed, Arnt and Skarsfeld [1998] noted that it is not clear which human cognitive functions correspond to the learning and cognitive functions assessed in the various behavioral models. Although such correspondence can be deduced, undoubtedly the best solution to this problem is to develop rodent models that are based on behavioral paradigms that can be used in both rats and humans and that can be shown to behave similarly in both species, as well as to exhibit parallel abnormalities in the rat model and in the modeled disorder. If these criteria are fulfilled, specific and selective effects exerted by APDs in such models offer an additional advantage, namely, they allow the elucidation of the neural and cognitive mechanisms that are directly (e.g., without previous pharmacological manipulation) modifiable by APDs. This in turn may promote the understanding of their clinical action and the development of drugs that modify critical cognitive processes while not necessarily acting via the same neural mechanisms.

In view of the above, a valid behavioral model of APD action should possess the following characteristics:

1. The behavior assessed in the model has relevance to the clinical condition; simply put, a valid animal model of APD action should be a valid animal model of schizophrenia, and ideally, one that possesses face, construct, and predictive validity.
2. The behavioral paradigm used to index the action of APDs can be used in rats and humans.
3. The model is selective and specific to APDs differing in their in vitro and in vivo pharmacology.
4. The model can dissociate between typical and atypical APDs.
5. The model does not require previous pharmacological manipulations to manifest the behavioral index of antipsychotic activity.
6. The model can shed light on the mechanisms of action of APDs.

The latent inhibition (LI) model of antipsychotic drug action developed in our laboratory has aimed at fulfilling the above criteria.

LATENT INHIBITION

Many experiments in the field of animal learning have demonstrated that conditioning to a stimulus depends not merely on its current relationship with a reinforcer, but is affected by an animal's past experience with that stimulus. Latent inhibition (LI) is one case of such a general biasing effect of past experience: it indexes the deleterious effects of nonreinforced stimulus preexposure on the subsequent conditioning to that stimulus. LI is considered to index organisms' capacity to ignore insignificant stimuli, and as such has become of increasing interest to neuroscientists studying the neural processes underlying stimulus selectivity and competition between conflicting associations as well as modeling disorders in which such capacity is impaired, such as schizophrenia [Gray et al., 1991; Lubow, 1973, 1989; Lubow et al., 1981; Weiner, 1990, in press; Weiner and Feldon, 1997].

Although a variety of behavioral tasks and conditioning procedures are used to demonstrate LI, all of them share the basic procedure: In the first stage (preexposure), subjects from one group are repeatedly exposed to a stimulus that has no consequences, whereas the second group does not receive the stimulus. The preexposed stimulus is then used as a signal of a target event (e.g., reinforcement) for all subjects in the second stage (conditioning). LI consists of the fact that previous learning that a stimulus is inconsequential interferes with the expression of subsequent learning that the same stimulus predicts a significant consequence, which is manifested in poorer learning of the stimulus–target event association of the preexposed compared to the nonpreexposed group.

LI can be demonstrated in many different behavioral procedures, and in many mammalian species, including humans [Lubow, 1973, 1989; Lubow et al., 1981; Lubow and Gewirtz, 1995]. An extensive review of human LI data has concluded that LI is similar (e.g., sensitive to the same manipulations) in humans and animals, and can be viewed as reflecting the operation of analogous processes across species [Lubow and Gewirtz, 1995].

LATENT INHIBITION MODEL OF SCHIZOPHRENIA

The LI model of schizophrenia was introduced by Solomon et al. [1981] and Weiner et al. [1981, 1984, 1988], who proposed that disrupted LI may provide an animal model of the widely described failure of schizophrenic patients to ignore irrelevant stimuli [e.g., Bleuler, 1911; Kraepelin, 1919; McGhie and Chapman, 1961; Oades,

1982; Gjerde, 1983; Nuechterlein and Dawson, 1984; Venables, 1984; Anscombe, 1987; Cornblatt et al., 1989]. Given that the predominant hypothesis regarding the pathophysiology of schizophrenia stated that excessive DA neurotransmission in the forebrain contributes to schizophrenia [Snyder, 1976; Meltzer and Stahl, 1976], these authors showed that rats treated with the DA releaser amphetamine, which produces and exacerbates psychotic symptoms in humans, fail to show LI, i.e., learn about the preexposed stimulus as if it were novel. Solomon and Staton [1982] further showed that the locus of amphetamine-induced disruption of LI was the nucleus accumbens (NAC), the target of the mesolimbic DA system. This finding established an animal model that combined the most prominent neurochemical dysfunction implied in schizophrenia, and a widely described cognitive dysfunction of this disorder. The original demonstration of amphetamine-induced LI disruption has been often replicated [e.g., De la Casa et al., 1993a; Killcross and Robbins, 1993; Killcross et al., 1994a; Gosselin et al., 1996; Moran et al., 1996; Ruob et al., 1997; Weiner et al., 1996b, 1997a, 1997c]. Importantly, LI disruption is restricted to DA enhancement produced by low doses of amphetamine: high doses of this drug, as well as direct DA agonists such as apomorphine, leave LI intact [Weiner et al., 1987c; Feldon et al., 1991]. The extension of the LI model to the clinic has shown that LI is disrupted in acutely psychotic schizophrenic patients tested within the first weeks of the current episode of illness or being in an acute phase of an otherwise chronic disorder [Baruch et al., 1988a; Gray et al., 1992a, 1995a]. The initial study has also shown, using repeated testing in the same patients, that LI is absent in the first 2 weeks of a schizophrenic episode and is restored to more or less normal levels after 7–8 weeks of neuroleptic treatment. Interestingly, normal or even reinstated LI is found in some subsets of schizophrenic patients [Gray et al., 1995a; Swerdlow et al., 1996; Williams et al., 1998]. Second, it was shown that amphetamine-treated normal humans, like amphetamine-treated rats, are incapable of ignoring the preexposed stimulus [Gray et al., 1992b; Thornton et al., 1996]; moreover, as in the rat, this effect shows an inverse dose dependency in humans, with low but not high dose abolishing LI. In addition, it was shown that normal humans scoring high on questionnaires measuring schizotypy show reduced LI relatively to subjects with low schizotypy scores [De la Casa et al., 1993b; De la Casa and Lubow, 1994; Vaitl and Lipp, 1997; Baruch et al., 1988b; Braunstein-Bercovitz and Lubow, 1998; Della Casa et al., 1999]. These results strengthened the likelihood that the LI effect observed in the two species is indeed functionally and pharmacologically the same phenomenon.

Subsequent studies using systemic and intracerebral drug administration, in vivo microdialysis, c-fos immunohistochemistry, and lesions have supported the involvement of the dopaminergic system and in particular the NAC as well as of two major sources of input to the NAC, the hippocampus and the entorhinal cortex, in LI [Solomon and Staton, 1982; Christiansen and Schmajuk, 1993; Young et al., 1993; Honey and Good, 1993; Tai et al., 1995; Yee et al., 1995; Sotty et al., 1996; Weiner et al., 1996a, 1999; Gray et al., 1997; Coutureau et al., 1999, in press; Holt and Maren, 1999; Joseph et al., in press; for reviews, see Weiner, 1990; Gray et al., 1995b; Weiner and Feldon, 1997; Weiner, in press]. This has been taken as further support for the validity of the LI model because it is consistent with the temporal lobe and mesolimbic DA pathology implicated in schizophrenia [e.g., Weinberger, 1987; Csernansky et al., 1991]. Importantly, lesion studies showed that LI can exhibit two opposite poles of abnormality, namely, to be disrupted under conditions that produce it in normal rats, and to persist under conditions that disrupt it in normal rats. The two aberrations, which can be seen as reflecting attentional overswitching and attentional perseveration, follow lesions to the two NAC subregions, shell and core, with the former disrupting LI and the latter leading to persistent LI [Weiner et al., 1999; Gal, 2000], and the same dissociation is found between the effects of cell lesions to the entorhinal cortex [LI disruption; Yee et al., 1995; Coutureau et al., 1999, in press] and the hippocampus [LI persistence; Honey and Good, 1993; Holt and Maren, 1999; see Weiner and Feldon, 1997; Weiner, in press]. LI also had been shown to be sensitive to manipulations of the serotonergic system [Asin et al., 1980; Solomon et al., 1978, 1980; Cassaday et al., 1993b], and the interest in the role of this system in LI has been recently renewed in the context of research on atypical APDs [Cassaday et al., 1993a; Hitchcock et al., 1996; Moser et al., 1996]. Finally, consistent with a neurodevelopmental hypothesis of schizophrenia [e.g., Weinberger and Lipska, 1995], LI was shown to be sensitive in an age- and gender-dependent manner to environmental and lesion manipulations during the vulnerable period of neonatal development [e.g., Grecksch et al., 1999; Shalev et al., 1998; Weiner et al., 1987b].

LATENT INHIBITION MODEL OF ANTIPSYCHOTIC DRUG ACTION

Latent Inhibition Procedure

The Tel-Aviv laboratory measures LI in an off-baseline conditioned emotional response (CER) procedure using water licking as the operant response. The LI procedure consists of three stages, each given on a different day: preexposure, in which the stimulus preexposed (PE) group receives a series of tones while the other, nonpreexposed (NPE) group spends an equivalent amount of time in the operant chamber without receiv-

ing the stimuli; conditioning, in which all of the rats receive a predetermined number of tone-footshock pairings; and test, in which the magnitude of conditioning to the tone is assessed in all rats by the degree of suppression of drinking during tone presentation. LI consists of the fact that the PE rats show a significantly lower suppression of drinking than their NPE counterparts.

Before the beginning of the LI procedure rats are trained to lick in the experimental chambers (baseline). Preexposure and conditioning are conducted 24 h apart and are given "off-baseline", namely, rats have no access to water. In addition, we interpolate a day of drinking (re-baseline) between conditioning and test. Drugs are administered in preexposure and/or conditioning only. The advantage of the off-baseline CER procedure is that the rat is not required to perform an overt response during preexposure and conditioning, and this allows elucidation of drug effects on LI unconfounded with their motor effects. In addition, because the test is removed from the stages of drug administration and is conducted without drugs, the effects of drugs are confined to the preexposure and/or conditioning stages. Most of the studies investigating the effects of APDs on LI use the CER procedure, typically very similar to that established at the Tel-Aviv laboratory, or a two-way active avoidance procedure, in which LI is reflected in poorer avoidance learning of the PE as compared to the NPE rats.

Reversal of Amphetamine-Induced Latent Inhibition Disruption

Both typical and atypical APDs reverse amphetamine-induced disruption of LI [Solomon et al., 1981; Warburton et al., 1994; Weiner et al., 1994; Gosselin et al., 1996; Moran et al., 1996; Moser et al., 1996]. Indeed, because LI disruption is obtained with low but not high doses of amphetamine, it is apparently well suited to pick up the effects of atypical APDs, which inhibit selectively the effects of low but not high amphetamine doses [Arnt, 1995; Arnt and Skarsfeldt, 1998]. Although the demonstration of such a reversal may be considered as a necessary requirement for the LI model of schizophrenia, and would be considered by many as a valid model of APD action, this is a drug–drug model, and as such has all the disadvantages of such models detailed above. Our aim was to establish whether the LI model can detect antipsychotic potential without requiring previous pharmacological manipulations.

Latent Inhibition Potentiation

We were the first to show that haloperidol (0.1 mg/kg, a dose that selectively blocks D2 receptors), given on its own, produces in LI a mirror effect of amphetamine, namely, potentiates the phenomenon. Using 40 tone preexposures and 2 conditioning trials, we showed that following haloperidol administration in both the preexposure and conditioning stages, the preexposure effect was significantly larger in haloperidol-treated compared to nontreated controls. Moreover, we showed that haloperidol potentiated LI also under conditions that did not yield LI in controls. For this, we reduced the number of preexposures to a level that did not produce LI in controls (10), and showed that haloperidol given in both stages promoted the expression of the preexposure effect under this condition, yielding LI [Weiner and Feldon, 1987].

Further studies showed that haloperidol-induced potentiation of LI is obtained also with repeated (5, 7, and 14 days) administration, and that doses of haloperidol that potentiated LI corresponded with their clinical potency [Christison et al., 1988; Dunn et al., 1993]. Moreover, Dunn et al. [1993] showed that LI enhancement with low number of preexposures is specific and selective for structurally diverse drugs with known antipsychotic efficacy and is not produced by a wide range of nonantipsychotic drugs. These authors concluded that "there is no animal model that better fulfills the criteria for predictive validity for antipsychotic effects" (p. 321). However, the Dunn et al. study yielded one false negative, namely, clozapine. Although this finding threatened to undermine the validity of the LI model and to limit considerably its utility as a screening tool for detecting antipsychotic potential of drugs, we and others have shown that clozapine produces in the LI model the two effects characteristic of typical APDs, namely, antagonizes amphetamine-induced disruption of LI and potentiates LI after low number of preexposures [Moran et al., 1996; Weiner et al., 1996b; Trimble et al., 1998; Shadach et al., 1999, in press]. LI potentiation with low number of preexposures has been shown for additional typical and atypical APDs as well as for putative antipsychotic agents [Feldon and Weiner, 1991; Weiner et al., 1992, 1994; Killcross et al., 1994b; Trimble et al., 1997; Gracey et al., 2000; Millan et al., 2000a, 2000b]. We have designed an additional LI procedure that reveals APD-induced potentiation, namely, one that uses a conventional number of preexposures (40) followed by a high number of conditioning trials (5). With these parameters, control rats do not display LI, whereas rats treated with haloperidol or clozapine do [Weiner et al., 1997b, Shadach et al., 1999, in press].

Studies assessing APD potentiation typically use drug administration in both the preexposure and conditioning stages. However, because LI involves the acquisition of two independent contingencies in preexposure (stimulus–no event) and conditioning (stimulus–reinforcement) [Weiner, 1990], a given drug can affect LI via preexposure, via conditioning, or via both, and may even exert opposite effects on LI in each of the stages (see next section). Consequently, the elucidation of the mecha-

nism/site of action of the drugs, and more importantly, the dissociation between the actions of different drugs, requires drug administration confined to each of the stages. Guided by this approach, we showed that haloperidol-induced potentiation of LI does not occur in the preexposure stage. Thus, rats preexposed under haloperidol but conditioned without it, showed a normal, nonpotentiated LI effect [Weiner et al., 1987a]. This was interpreted by us to imply that haloperidol does not affect the acquisition of the stimulus–no event contingency in preexposure, but promotes the expression of this contingency in conditioning [Weiner, 1990]. Consistent with the latter suggestion, Peters and Joseph [1993] showed that after low number of preexposures that did not produce LI in controls, administration of haloperidol confined to conditioning, led to the emergence of LI. Likewise, we showed that with 40 preexposures and 5 conditioning trials, rats treated with haloperidol or clozapine only in conditioning persisted in showing LI [Weiner et al., 1997b]. We have recently tested [Shadach et al., 1999] the effects of clozapine (2.5, 5, and 10 mg/kg) on LI using the two sets of parameters that do not yield LI in control rats (10 preexposures and 2 conditioning trials and 40 preexposures and 5 conditioning trials), and what we call a "drug–no drug design", namely, clozapine administration in either the preexposure stage, the conditioning stage, or in both. As expected, no LI was evident in vehicle-treated rats under both sets of parameters. Likewise, no LI was evident in rats that received clozapine only in the preexposure stage. In contrast, with the exception of the low dose at the 40 PE + 5 trials condition, clozapine administered in the conditioning stage, irrespective of drug condition in preexposure, led to the emergence of LI. These results demonstrated conclusively that the site of APD-induced LI potentiation is the conditioning stage [for theoretical implications, see Weiner, 1990, in press; Weiner and Feldon, 1997].

The most likely neural mechanism underlying the LI potentiating effect is blockade of D2 receptors, which is shared by typical and atypical APDs. However, clozapine produces weaker D2 blockade compared to typical APDs [Meltzer, 1989; Brunello et al., 1995; Kinon and Lieberman, 1996; Arnt and Skarsfeldt, 1998], indicating that low D2 receptor occupancy suffices for LI potentiation, as it suffices for an antipsychotic action. As for the neural site of DA blockade that subserves LI potentiation, Gray et al. [1997] and Joseph et al. [in press] showed that the LI potentiating effect of haloperidol is mediated via the NAC: After 10 preexposures, NAC vehicle-injected rats did not show LI, whereas an intra-accumbens injection of haloperidol led to the emergence of LI. Intra-accumbens injection of haloperidol also reversed the disruption of LI caused by systemic amphetamine administration. Importantly, both the potentiating and the amphetamine-reversing effects were obtained with haloperidol injection confined to the time of conditioning.

Finally, the extension of this line of research to normal humans has shown that, like in the rat, LI is potentiated by haloperidol [Williams et al., 1996, 1997], supporting the commonality of underlying cognitive and neural mechanisms in the two species.

Dissociation Between Typical and Atypical Antipsychotic Drugs in the Latent Inhibition Model

Extending our approach of manipulating preexposure and conditioning parameters in combination with drug–no–drug administration regimen, we have recently demonstrated that the LI model can dissociate between typical and atypical APDs [Shadach et al., in press]. Our experiments were based on the following rationale.

While atypical APDs are characterized by a broad receptor profile, their mixed D2–5-HT2 receptor antagonism has been the feature most often suggested to account for their greater antipsychotic efficacy in general, and their efficacy in improving negative symptoms in particular [e.g., Meltzer, 1989; Leysen et al., 1993; Brunello et al., 1995; Schotte et al., 1996; Arnt and Skarsfeldt, 1998]. The serotonergic component of atypicality is particularly relevant to LI, because LI is disrupted by brain serotonin depletion [Asin et al., 1980; Cassaday et al., 1993b; Lorden et al., 1983; Solomon et al., 1978, 1980], as well as by systemic administration of the 5-HT2 antagonist, ritanserin [Cassaday et al., 1993a]. In spite of this, there has been no evidence that atypical APDs disrupt LI. Because serotonergic antagonists disrupt LI when given in both the preexposure and conditioning stages [Cassaday et al., 1993a], and atypical APDs potentiate LI when given in conditioning but not when given in preexposure [Weiner et al., 1997b; Shadach et al., 1999], it follows that if atypical APDs disrupt LI via serotonergic antagonism, the site of such an effect must be the preexposure stage; in addition, it is clear that the demonstration of LI disruption requires the use of preexposure and conditioning parameters, which yield LI in controls.

We therefore tested the effects of haloperidol (0.1 mg/kg) and clozapine (5 mg/kg), as well as of the selective 5-HT2 antagonist, ritanserin (0.6 mg/kg), on LI, using two sets of conditions: 40 preexposures and 5 conditioning trials, which do not lead to LI in control rats, and 40 preexposures and 2 conditioning trials, which produce LI in normal rats. We predicted and showed that:

1. With parameters that did not yield LI in controls, both haloperidol and clozapine were without an effect when administered in preexposure and potentiated LI when administered in conditioning and in both stages, whereas ritanserin

was ineffective in all three administration conditions.
2. With parameters that led to LI in controls, haloperidol was without an effect in all three administration conditions; clozapine had no effect when administered in conditioning and in both stages but disrupted LI when administered in preexposure; ritanserin had no effect when administered in conditioning but disrupted LI when administered in preexposure and in both stages [Shadach et al., in press].

These results provided the first demonstration that clozapine disrupts LI when given in preexposure. As for the mechanism of this disruptive action, it cannot stem from DA blockade, because DA mechanisms are not involved in preexposure; because the preexposure-based disruptive effect was also exerted by the selective 5-HT2 antagonist ritanserin, it is likely that clozapine-induced disruption is 5-HT2 mediated. In addition, the fact that clozapine disrupted LI via preexposure but spared LI when administered in both stages indicates that clozapine's action in conditioning overrode its disruptive effect in preexposure, implying that the 5-HT2 and DA2 antagonistic actions of clozapine compete in LI, and that the manifestation of such a competition is dependent on the parameters of the LI procedure. In addition, because the relative potency of the two actions are dose dependent, with 5-HT2 receptor occupancy predominating at lower doses and DA2 receptor occupancy occurring at higher doses [Schotte et al., 1996], the effects of clozapine and other atypical APDs on LI should be dose dependent. Thus, depending on the parametric conditions and doses of clozapine, the serotonergic component should be able to override the dopaminergic component, or vice versa, leading to either potentiated LI, intact LI, or disrupted LI. This may explain why clozapine-induced potentiation of LI is obtained within a relatively narrow dose range [Moran et al., 1996; Trimble et al., 1998].

We have now completed experiments with additional doses of clozapine and haloperidol and with additional atypical APDs, which replicated the selective preexposure-based LI-disrupting capacity of atypical APDs and in addition, supported the notion that the effects of these drugs when administered in both preexposure and conditioning depend on their 5-HT2–DA2 ratio [unpublished data].

LATENT INHIBITION FORCED-SWIM TEST MODEL

Driven by the interest to develop screening tests that can dissociate between typical and atypical APDs as well as by our emerging concept that such a dissociation can be best achieved by determining patterns of behavioral drug action rather than isolated effects on one behavioral test, we have recently begun to investigate the potential of the FST. FST is the most widely used rat model of depression in which immobility is considered to reflect a state of despair in the rat [Porsolt et al., 1977]. Our interest in this model has stemmed from several sources:

1. It has been noted often that negative symptoms overlap with depressive symptoms [Lindenmayer and Kay, 1989; Bermanzohn and Siris, 1992; Rao and Moller, 1994; Malla, 1995; Collins et al., 1996; Sax et al., 1996].
2. Atypical APDs such as clozapine and olanzapine, which display a superior efficacy in the treatment of negative symptoms, have an antidepressant activity [Ranjan and Meltzer, 1996; Tollefson et al., 1998], suggesting that antidepressant-like action may distinguish atypical from typical APDs.
3. This difference between the two classes of drugs in the clinic appears to be paralleled by their effects in the FST: thus, the typical APD, haloperidol, increases immobility, whereas the atypical APD clozapine either has no effect or decreases immobility [Browne, 1979; Borsini et al., 1984; Gorka and Janus, 1985; Kawashima et al., 1986].
4. Noda et al. [1995] showed that PCP-induced increase in immobility was reversed by atypical but not by typical APDs, and suggested that this can serve as a model of negative symptoms.

The above suggests that the FST model has a capacity to differentiate between typical and atypical APDs; however, it cannot dissociate between atypical APDs and antidepressant drugs, whose ability to decrease the duration of immobility is well established [e.g., Porsolt et al., 1977; Detke et al., 1995; Noda et al., 1997; Page et al., 2000]. Because LI potentiation is selective and specific for APDs, we reasoned that a combined FST–LI model could provide a tool that can dissociate between typical APDs, atypical APDs, and antidepressants. After pilot studies that showed that the FST can, in our experience, differentiate between clozapine and haloperidol, we tested haloperidol (0.1 mg/kg), clozapine (2.5 mg/kg), and the classic antidepressant imipramine (10 mg/kg) in the FST and in the LI procedure with 40 preexposures and 5 conditioning trials. We predicted and found that:

1. Haloperidol increased immobility in the FST and potentiated LI.
2. Clozapine decreased immobility in the FST and potentiated LI

3. Imipramine decreased immobility in the FST while having no effect on LI [unpublished data].

These results indicate that the combined LI–FST model may indeed have the potential to differentiate between the three classes of drugs. Clearly, this has to be tested with additional doses and drugs, particularly additional antidepressants, because to date only imipramine has been tested in LI.

LESION-BASED MODELS

Lesion-based models have an advantage over pharmacological models in that they provide more precise information (compared to systemic drug administration) on the site of the damage that leads to the behavioral aberration alleviated by the APD treatment, although it should be borne in mind that such models do not provide information on the site at which the drugs act to reverse the deficit. To date, LI disruption produced by different lesions (i.e., conventional hippocampal lesion, excitotoxic entorhinal cortex lesion, and electrolytic shell lesion) has been shown to be reversible with haloperidol [Christiansen and Schmajuk, 1993; Yee et al., 1995; Weiner et al., 1996a]. Because behavioral deficits that are blocked by a typical APD are likely to be blocked also by atypical APDs, one could expect that lesion-induced LI disruptions would not to be suitable to serve as models that dissociate between the two classes of drugs. However, Coutureau et al. [in press] have reported that LI disruption caused by an excitotoxic entorhinal cortex lesion was reversed by olanzapine but not by haloperidol, suggesting that LI disruption after damage to some regions might be selectively sensitive to atypical APDs.

In view of the findings that perturbations of some brain regions can lead to LI persistence rather than disruption (see above), and given our finding that atypical but not typical APDs disrupt LI via preexposure, we expected that lesion-induced LI persistence might be normalized by atypical but not typical APDs. We have recently tested this possibility using excitotoxic core NAC lesion. We found that core lesion–induced LI persistence with a high number of conditioning trials was reversed by clozapine administered in preexposure but was not affected by its administration in conditioning. Furthermore, we found that core lesion also increased immobility in the FST and produced perseveration in discrimination reversal, and that the latter two deficits were alleviated by clozapine but not by haloperidol [unpublished data]. These results provide additional support for the validity of a combined LI–FST model and suggest that core lesion–induced LI aberrations coupled with other behavioral deficits produced by this lesion may serve as a model that dissociates between typical and atypical APDs.

NEURODEVELOPMENTAL BEHAVIORAL MODELS

An additional approach to the development of behavioral models relies on purely behavioral infant manipulations that lead to the desired deficits at adulthood. This approach has a double advantage of being nonpharmacological as well as consistent with the widely accepted neurodevelopmental hypothesis of schizophrenia [Weinberger and Lipska, 1995]. Thus, rats reared in isolation show PPI deficits in adulthood that are reversed by both typical and atypical APDs [Bristow et al., 1995; Varty and Higgins, 1995]. LI has been shown to be sensitive to various perinatal manipulations, such as prenatal stress and postnatal nonhandling and isolation [Weiner et al., 1985, 1987b; Feldon and Weiner, 1988, 1992; Feldon et al., 1990; Shalev et al., 1998]. These early manipulations can give rise either to LI disruption or persistence. To date, only one study tested the effects of APD treatment in such neurodevelopmental models. This study showed that LI disruption in adult male rats that were nonhandled in infancy is reversed by haloperidol [Feldon and Weiner, 1988, 1992]. This suggests that this particular model may not be able to dissociate between typical and atypical APDs.

Given the often-stressed association of schizophrenia with exposure in utero to viral infections and the findings of immune abnormalities in schizophrenic patients [Mednick et al., 1988; Torrey, 1991; Altamura et al., 1999], we tested the effects of prenatal administration of the synthetic double-stranded RNA polyriboinosinic-polyribocytidilic acid (Poly I:C), which simulates an in vivo viral response (produces cytokines and interferons in mammalian cells), on LI in the offspring. The male offspring of rats that were injected with Poly I:C on days 15 and 17 of pregnancy failed to show LI at 3 months. In addition to LI disruption, these rats showed decreased immobility in the FST and facilitated reversal, consistent with our previous pattern of results, in which LI persistence was paralleled by increased immobility in the FST and perseveration in reversal. We have some preliminary indication that these deficits may be reversed by clozapine but not by haloperidol.

SUMMARY

In view of the above, it appears that the LI model fulfills all of the criteria for a valid behavioral model of APD action outlined at the outset of this article, as detailed below.

1. LI measures a cognitive process that is known to be impaired in schizophrenia, namely, the ability to ignore stimuli that had been inconsequential in the past. Indeed, beginning with Kraepelin's [1919] observation that a "disorder of attention" is "conspicuously developed" in

patients with dementia praecox, and Bleuler's [1911] analogous description of schizophrenia as the loss of "selectivity which normal attention ordinarily exercises among the sensory impressions," attentional deficit in schizophrenia, most often described as an inability to filter out or ignore irrelevant or unimportant stimuli, has retained its centrality in numerous theoretical formulations, and it has been argued that the major abnormalities of schizophrenia can be derived from this single underlying deficit. The findings of disrupted LI in some subsets of schizophrenic patients are consistent with this formulation and lend the LI model construct validity. It should be pointed out that based on the findings that lesions to some brain areas (see above), as well as DA blockade, produce an abnormally persistent LI, we also suggested that spared or reinstated LI found in some subsets of schizophrenic patients reflects an attentional deficit but of an opposite nature, namely, an inability to dis-ignore an irrelevant stimulus, or attentional perseveration [Weiner and Feldon, 1997; Weiner, in press].

2. The LI paradigm can be studied using similar procedures in rats and humans, and reflects the operation of analogous processes across the two species. Moreover, the demonstrations that in normal humans, as in the rat, LI is disrupted by amphetamine and potentiated by haloperidol, support the commonality of underlying neural mechanisms in the two species.
3. The model predicts antipsychotic activity for both typical and atypical APDs differing in their in vitro and in vivo pharmacology and it detects antipsychotic potential with both acute and repeated drug administration.
4. The model dissociates between typical and atypical APDs, so that a) both classes of drugs potentiate LI via their action at the conditioning stage under conditions that do not lead to LI in controls, and b) atypical but not typical APDs disrupt LI via action at the preexposure stage under conditions that lead to LI in controls. In addition, the results suggest that the LI potentiating and disrupting effect of atypical APDs may be due to their D2 and 5-HT2 antagonism, respectively. It should be noted that the nature of the dissociation in the LI model differs from that in other behavioral models claimed to model processes impaired in schizophrenia (PCP-induced disruption of PPI and of social interaction). Thus, the dissociation between typical and atypical APDs in the above models consists of ineffectiveness of typical versus effectiveness of atypical APDs, whereas in the LI model, both classes of APDs are effective but in a differential manner.
5. APDs-induced potentiation of LI is specific and selective for APDs and is not produced by a wide range of nonantipsychotic agents. In addition, LI is the only model in which APDs produce improved performance. As pointed out by Arnt and Skarsfeldt [1998], most behavioral animal models have little chance to yield such effects because cognitive performance is near optimal in normal rats. The advantage of the LI procedure is that solely by means of parametric manipulations, we can produce "poor performance" in controls on the background of which the facilitatory effects of APDs are revealed.

The specificity and selectivity of atypical APD-induced disruption of LI is not known at present. However, it should be emphasized that our modeling stresses a pattern of drug effects rather than isolated actions; thus, an atypical APD must disrupt LI via preexposure *and* potentiate LI via conditioning. If a given drug disrupts LI via preexposure but does not potentiate it via conditioning, it will not qualify as an atypical APD, as was the case with ritanserin in our studies.

6. The LI model does not rely on pharmacological means to elicit the behavioral index of antipsychotic activity and to differentiate typical from atypical APDs. Thus, the model does not require previous administration of DA agonists or other drugs for the manifestation of both the potentiating and the disruptive actions of APDs, but detects them with parametric manipulations of the LI procedure. This implies that LI involves neural and cognitive processes that are directly and differentially modifiable by typical and atypical APDs. It remains to design an LI procedure that will simultaneously tap both the disruptive and the potentiating effects of atypical APDs using the same preexposure and conditioning parameters.
7. The model has shed light on the mechanism of the potentiating action of APDs, namely, that this effect is mediated via DA blockade in the NAC during conditioning. The mechanisms underlying the recently revealed disruptive effect of atypical APDs are not yet clear, except that it is confined to preexposure and is likely to be caused by 5-HT2 antagonism.
8. Our demonstration of a dissociation between haloperidol, clozapine, and imipramine in the combined LI–FST model indicates that the utility of the LI model can be further extended when it is

combined with other models that are sensitive to different aspects of the atypical APD action, i.e., their antidepressant-like activity. It should be noted that although the effects of each of the drugs in each of the two models have been shown before, it is the combined pattern of their effects in both models that reveals a unique behavioral "fingerprint" that allows the dissociation between their modes of action. Moreover, also the combined LI–FST model does not require previous drug administration to obtain the three-way dissociation. The latter is of particular importance because in previous work, a dissociation between typical and atypical APDs in the FST was deemed to require PCP administration [Noda et al., 1995], and moreover, reversal of PCP-induced increase in immobility did not differentiate between atypical APDs and at least some antidepressants [Noda et al., 1997]. Our results show that a nonpharmacological FST behaves like a pharmacological one, i.e., dissociates between typical and atypical APDs, but not between the latter and antidepressants, and that addition of a nonpharmacological model that is specific and selective for APDs may not only solve the confounding inherent in the FST but may allow the differentiation between the three classes of drugs.

9. Finally, the use of the LI model in rats that sustain lesions or other physiological manipulations (e.g., stimulation) of specific brain regions may provide clues as to the relationship between the effects of these drugs and the site of brain damage, and possibly reveal differential effects of typical and atypical APDs depending on the site of the damage. Although data on this are sparse (see Lesion-Based Models above), they raise the possibility that a) LI disruption caused by different lesions will be reversed by APDs administered in conditioning (it is not clear at present whether such reversal will be obtained with both typical and atypical APDs or selectively with atypical APDs depending on the damage site), and b) LI persistence caused by different manipulations of different brain regions will be selectively reversed by atypical APDs administered in preexposure.

An additional point is in order here: As evidenced from our experiments with core-lesioned rats, a lesion that leads to LI persistence leads to additional behavioral alterations (in our case, increased immobility in the FST and perseveration in reversal) that are also differentially sensitive to typical and atypical APDs. Although this can be taken as a strength of a lesion model, it robs the LI model of its uniqueness as a selective and specific behavioral model. This is not surprising, because "lesion models" are open to the same criticism we raised above with regard to "drug models," namely, that the "model" is the manipulation rather than the specific behavior assessed.

It is commonly asserted that both typical and atypical APDs are effective against positive symptoms, whereas atypical APDs have higher efficacy for negative symptoms/treatment-resistant schizophrenia, and that therefore, an animal model that is sensitive to both classes of APDs may have predictive validity for the former condition, whereas a model that is sensitive to atypical but not to typical APDs may have predictive validity for the latter condition(s) [Arnt and Skarsfeldt, 1998; Brunello et al., 1995; Kinon and Lieberman, 1996]. Viewed in this light, LI potentiation may have predictive validity for the treatment of positive symptoms, and LI disruption may have predictive validity for the treatment of negative symptoms/treatment-resistant schizophrenia. The latter is also congruent with the claim that D2 antagonism is effective for treating positive symptoms and that 5-HT2 antagonism plays a role in the alleviation of negative symptoms [Leysen et al., 1993; Meltzer, 1989; Schotte et al., 1996]. Likewise, the differential effects in the combined LI–FST model indicate that LI potentiation combined with increased immobility may have predictive validity for the treatment of positive symptoms, whereas LI potentiation combined with decreased immobility may have predictive validity for the treatment of negative symptoms/treatment-resistant schizophrenia, while at the same time allowing the dissociation between atypical APDs and antidepressants. Finally, if future studies support our suggestion that LI disruption caused by different manipulations (be they lesions, stimulation, perinatal treatments) is reversed by both typical and atypical APDs given in conditioning, whereas LI persistence caused by different manipulations is reversed by atypical APDs given in preexposure, then the former will have predictive validity for the treatment of positive symptoms and the latter will have predictive validity for the treatment of negative symptoms/treatment-resistant schizophrenia. In addition, such findings may imply that regions whose perturbations lead to LI disruption may be implicated in the positive symptoms of schizophrenia, whereas regions whose perturbations lead to LI persistence may be implicated in the negative symptoms of schizophrenia.

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