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Behavioural Sensitization in Addiction, Schizophrenia, Parkinson´s Disease and Dyskinesia

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Incentive learning takes place when dopaminergic neurons are activated, usually by rewards. As a result, previously neutral stimuli associated with reward acquire incentive salience and thus the ability to elicit approach or other responses in the future. Incentive learning is assumed to underlie psychostimulant-induced context-dependent sensitization that may play a prominent role in the development of addiction, in dyskinesia, and in amphetamine-induced psychosis. Assuming that these pathological states are due to the gradual process of sensitization, the effects of therapeutics might be manifested as a gradual desensitization. This assumption could explain the delay between onset of cellular effects of drugs (*e.g.*, dopamine receptor blockade) and the improvement in symptoms (*e.g.*, decreases in psychotic symptoms).

Reduced dopamine activity results in behavioural changes that are opposite to psychostimulant-induced sensitization, *i.e.*, rewarded behaviours decline in an extinction-like fashion despite the presence and consumption of rewards. We show here that also non reward-related behaviour, *i.e.*, motor activity and catalepsy, follows the same rules: Motility is not switched off by dopamine receptor blockade or by 6-hydroxydopamine lesions, but shows a test-to-test extinction-like decline. Thus, psychostimulant-induced sensitization and dopamine-deficiency induced decline of behaviour follows similar rules but in opposite directions.

Keywords: Addiction; Catalepsy; Dyskinesia; Incentive learning; Parkinson's disease; Schizophrenia; Sensitization

INTRODUCTION

The behavioural effects of some neurotropic drugs occur over days or weeks, although their action at receptors takes place within hours. For example, there is a delay of weeks between the onset of dopamine receptor-blockade and improvement in psychosis (Reynolds, 1992). It will be discussed here that behavioural sensitization may play a crucial role in the development of various psychiatric and also in neurological diseases and that a therapy can not switch off the pathological symptoms instantaneously, but has to induce a desensitization process which takes some time.

Sensitization is defined as the augmentation of behaviour upon repeated administration of a drug. It occurs with psychostimulant drugs and is believed to be due to enhancement of dopamine activity in the ventral tegmental area and the nucleus accumbens (for review see Tzschentke and Schmidt, 2003; Hyman, 2005). Sensitization is associated with an increase in synaptic spine density in the core (but not in the shell) of the nucleus accumbens (Li *et al.*, 2004). Once sensitization has taken place, there is a memory for the context eliciting the sensitized response. Here, sensitization will be considered to result from dopamine-mediated incentive learning. Incentive learning takes place when dopamine neurons are activated, usually by rewards, and results in the acquisition by previously neutral stimuli associated with reward of an enhanced ability to elicit approach and other responses in the future. This learning will lead to an augmented response with repeated pairings of the same stimuli with reward (Beninger, 1983; Beninger *et al.*, 1999). There also may exist context-independent sensitization, which is non-associative, but this form of sensitization will not be discussed here.

ADDICTION

The development of addictions can be understood as resulting from a learning process labled reward-

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related incentive learning. The mechanism underlying incentive learning is thought to be a dopamine-mediated change in the strength of glutamatergic synapses (Beninger and Gerdjikov, 2004; 2005). The influential work of Robinson and Berridge (1993) is based on psychostimulant-induced sensitization and states that by way of sensitization, drug-associated cues become incentive salient stimuli up to the point at which they become so powerful that they gain control over voluntary behaviour. In other words, a sensitization process, induced by repeated ingestion of psychostimulants, leads to the development of compulsivity (see also Baker and Kalivas, 2005). The view that sensitization is associated with addiction is further supported by the following findings:

1) Sensitization includes the formation of memory that is very stable against forgetting or extinction. In the rat, sensitized locomotor activity can persist for over one year after the end of drug administration.

2) The degree of sensitization determines the vulnerability for relapse, *i.e.*, strongly sensitized animals relapse more frequently that weakly sensitized animals.

3) Sensitization facilitates subsequent drug taking, for example amphetamine or cocaine pretreatment facilitated the development of cocaine self-administration.

4) As is the case for human addiction, the degree of sensitization varies considerably from individual to individual (for a review of these points, see Tzschentke and Schmidt, 2003).

Several therapeutic concepts for the treatment of addiction exist: The concept of a simple operant conditioning as the basis of addiction and punishment as a therapy of addictive behaviour has basically failed. However, the concept that addiction is incentive learning *i.e.*, sensitization, is very attractive but this infers that a therapy of addiction should consist of an incremental devaluation of stimuli supporting a habit and/or a sensitized response.

Despite the well-established role of dopamine in incentive learning and sensitization, medications that decrease or inhibit dopamine activity have failed so far (although in recent studies dopamine D_3 receptor antagonists have shown promise, as reviewed by Heidbreder *et al.*, 2005). However, as pointed out above, the glutamatergic input to the dopamine system is crucial for context-induced sensitization (Tzschentke and Schmidt, 2003). Thus, evidence has accumulated that reducing glutamatergic activity may be promising in the treatment of context-induced relapse and addiction. Several NMDA or mGluR5 receptor-antagonists have been proven to be effective, but their use in humans is limited because of side effects. However acamprosate, which is a weak NMDA - as well as a mGluR5 - antagonist, has proven useful in the treatment of alcohol addiction (Mann, 2004).

SCHIZOPHRENIA

The classical antipsychotics are believed to act mainly through dopamine D_2 receptor- blockade, inferring that an abnormally active dopamine system underlies psychosis. However the problem for some has been that dopamine receptor-blockade occurs within hours, whereas the onset of the antipsychotic response is delayed by days or weeks. This temporal discrepancy has been linked to changes in dopamine metabolism in various brain structures, and to depolarization block of dopaminergic neurons. However there is still no consistent theory and a number of possibilities have been discussed (for review see Reynolds, 1992). The temporal discrepancy might be explained by assuming that schizophrenia is also due to a sensitization process mediated by incentive learning. There is much evidence for this assumption at least for the positive symptoms of schizophrenia: Usually, before the outbreak of full blown psychosis, *i.e.*, during the prodromal phase, patients report experiences of enhanced awareness, of an increased perception of novelty, of attribution of salience to previously neutral stimuli (McGhie, 1977). Following on the work of Beninger (1983; 1988), Kapur (2004) postulated "…. that during the prodrome there is a context-independent or context inappropriate firing of dopamine-containing neurons and subsequent dopamine release. This produces a perplexing sense of novelty in patients…" (p. 403). During the further course of the disease, the patient develops delusions in an attempt to explain the aberrant novelty and salience experiences. Thus, in schizophrenia excessive activity in dopamine systems leads to excessive incentive learning, sensitizing the individual to environmental stimuli that normally would be neutral. Normal brain processes may attempt to make sense of these apparently important stimuli leading to delusions. In drug addictions, stimuli associated with drug taking and activation of the dopamine system may, through the same type of sensitization mechanism, come to be powerful incentive stimuli controlling behaviour and possibly giving rise to delusions.

According to the outlined view, antipsychotics do not instantaneously switch off the positive symptoms. Rather, by blocking dopaminergic transmission they create the conditions that lead to a gradual reduction in the salience of stimuli and with each further encounter with those stimuli, the salience is further decreased. This process is analogous to the gradual extinction of responding to a reward-related cue when that cue is no

longer followed by reward. By way of this process of devaluation of salience, antipsychotics produce their gradual onset of action leading to a remission of positive symptoms.

When amphetamine is taken chronically, it can induce a psychotic state resembling schizophrenia (Snyder, 1972). Kalivas *et al.* (1999) comprehensively discussed the issue of whether there is a role for sensitization in psychostimulant-induced paranoia and psychosis. He concluded that "…within the population of psychostimulant addicts the production of paranoia and psychosis clearly shares characteristics of behavioural sensitization, including, 1) the necessity for prolonged psychostimulant abuse before the appearance of psychosis, 2) the induction of relapse psychosis by lower doses of amphetamine than those required for initial psychosis, and 3) the occurrence of drug abstinence, indicating an enduring change in the nervous system." Further, chronic administration of amphetamines produces an increase in aggression and it may be worth investigating whether or not this also represents a phenomenon of sensitization.

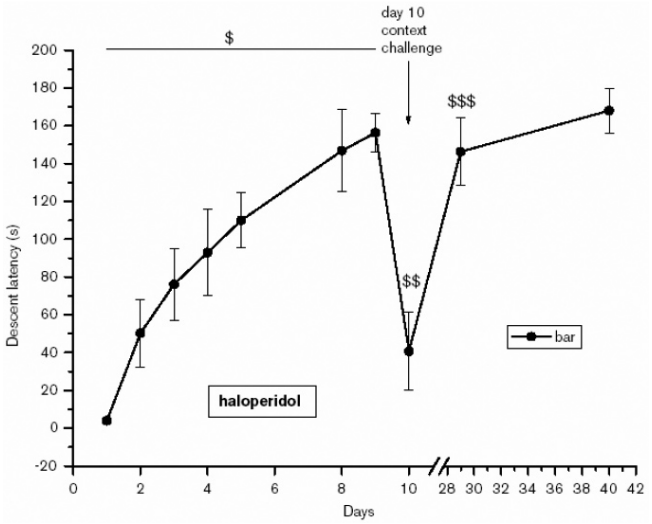

FIGURE 1, Experiment 1 Catalepsy-testing; intermittent haloperidol administration. On each experimental day the subjects received a haloperidol injection (0.25 mg/kg body weight). The catalepsy testing was carried out in context A (days 1-5, 8-9, 29, 40) and in context B (context challenge on day 10). Development of intensification of catalepsy occurred in context A from days 1 to 9 ($: P <0.01). The context-challenge (context B) showed a decrease of descent latency ($$: P <0.01). On day 29 (context A) the rats showed a strong increase compared to day 10 ($$$: P <0.01).

PARKINSON`S DISEASE

Theoretically it may be postulated that reduced dopamine-activity results in behavioural changes that are opposite to sensitization. For reward-related incentive-learning this seems to be the case: Wise *et al.* (1978) showed that the dopamine D_2-like receptor blocker pimozide did not switch off behaviour after the first administration, but that lever pressing for food, or running for food, gradually declined from test to test in an extinction-like fashion despite the fact that the animals continued to receive food for lever pressing or running and continued to eat it. Thus, dopamine receptor blockade is functionally similar to omission of reinforcement (for review, see Wise, 2004).

Parkinsonian symptoms become intensified by repeated testing.

In the same manner that responding to stimuli associated with enhanced activation of the dopamine systems is seen to sensitize, increasing from trial to trial, we have found that responding to stimuli associated with decreased dopamine function also intensifies, *decreasing* from trial to trial. We treated rats with the dopamine receptor-blocking drug haloperidol (0.25 mg/kg i.p.) for 7 consecutive days. One hour after each treatment, the rats were tested for akinesia and rigidity (catalepsy). This threshold dose of haloperidol did not produce catalepsy in the first session but a test-to-test increase in catalepsy was observed (FIG. 1) (Schmidt *et al.*, 1999; Klein and Schmidt, 2003). This result has frequently been replicated (Lanis and Schmidt, 2001). An accumulation of haloperidol in body tissue or a role of depolarization block does not account for this effect, since the test to test increase does not occur when rats are treated in the same way but are not tested for catalepsy after each injection (Schmidt *et al.*, 1999, see also below under context dependency). Additionally, a test-to-test intensification of catalepsy has been demonstrated in rats that underwent 6-hydroxydopamine lesions (FIG. 2). The rats were lesioned bilaterally: 8 µg of 6-hydroxydopamine were infused at four sites into each striatum. Thereafter the rats recovered for five weeks. At this time the degeneration of dopaminergic neurons is completed. The treatment induced only mild catalepsy in the first test session (FIG. 2). However, from test-to-test in the same context (A), catalepsy intensified. The fact, that in context B the intensification was not expressed shows that intensification of catalepsy could not be due to further gradual degeneration of dopaminergic neurons. *Post mortem* neurochemical analysis (HPLC-EC) revealed a 45 % reduction of striatal dopamine (Klein and Schmidt, 2003).

What can this tell us about Parkinson's disease? The principles governing reward-related learning also apply to the dopamine deficiency state: Dopamine release

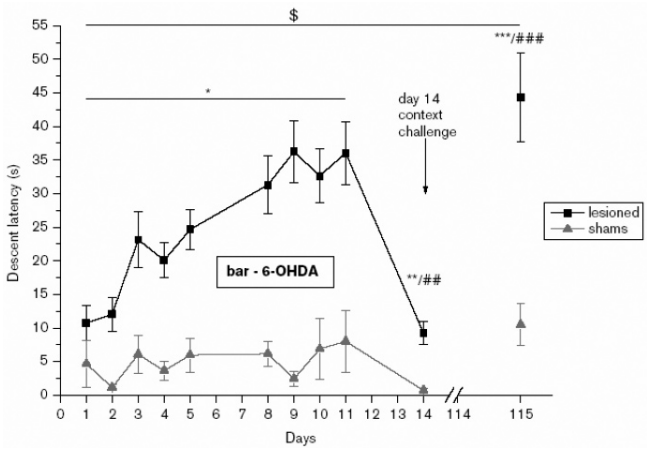

FIGURE 2, Experiment 2 Catalepsy-testing on the bar after 6-hydroxydopamine (6-OHDA) lesion and persistent dopamine (DA) depletion. The catalepsy testing was carried out in context A (days 1-5, 8-11 and 115) and in context B (context challenge on day 14). Development of sensitization occurred in the lesioned group in context A from days 1 to 11 (*: P <0.01). The context-challenge (context B) showed a decrease of descent latency for both groups (lesioned **: P <0.01; shams ##: P <0.05). On day 115 (context A) the rats showed a strong increase compared to day 14 (lesioned ***: P <0.01; shams ###: P <0.01). Data of both groups came from different populations ($: P <0.0001).

in the striatum is a positive learning signal leading to enhanced motor responses to stimuli associated with that dopamine release, *i.e.*, sensitization of behaviour. A dopamine deficiency, as is the case in Parkinson's disease, may produce an anti-reward signal, attenuating future responding to stimuli associated with that dopamine deficiency. This would produce the characteristic decline in motor responses. In this view, dopamine is a teaching signal: too much dopamine produces a test-to-test increase in behaviour; too little dopamine produces a test-to-test decrease in behaviour.

In an attempt to model incentive learning, McClure *et al.* (2003) used an algorithm based on the prediction error explanation of dopaminergic neuron response. This computational model describes sensitization phenomena and predicts that reducing dopamine activity does not immediately change behaviour but causes gradual extinction after repeated exposure. Our findings on the intensification of parkinsonian symptoms nicely fit these predictions.

Context Dependency of Parkinsonian Symptoms

The intensification of catalepsy is completely context/experience dependent, since it depends on the execution of cataleptic behaviour in the same environment. If rats were treated with haloperidol in the very same dose regimen, but were not tested for catalepsy, instead remaining in their home cages, they did not show intensification of catalepsy; others even reported on the development of tolerance towards the cataleptogenic effects of haloperidol (Schmidt *et al.*, 1999). The context-dependency of the intensified catalepsy can also be seen from figures 1 and 2. Catalepsy that has intensified in context A is only expressed in context A (days 1-9); if tested in context B (day 10, FIG. 1; day 14, FIG. 2), *i.e.*, in another room (but using the identical experimental set-up), the intensified catalepsy was not expressed.

These findings on catalepsy correspond with findings about psychomotor stimulant-induced sensitization. Context-independent and context-dependent sensitization are distinguished. Anagnostaras *et al.* (2002) investigated the role of the context upon amphetamine-induced sensitization. These authors postulated three memory mechanisms regulating the context-dependency of amphetamine sensitization:

1. Repeated drug administration induces sensitization of the neural substrate that mediates the unconditioned response to the drug, a form of non-associative learning.
2. A context where the drug is not expected can exert an inhibitory influence, blocking the expression of neural sensitization.
3. A context in which drug is expected can exert an excitatory conditioned response, amplifying the sensitized response.

Whereas amphetamine induces context-independent plus context-dependent sensitization,
there also exists completely context-dependent sensitization. This is the case with bromocriptine (Carlezon *et al.*, 1995) and this is also the case for intensified catalepsy. It is generally assumed that in this case, the association of the context in which the drug is expected facilitates expression of sensitization. However it has not been tested so far whether or not a new context inhibits the expression of the sensitized response.

The intensified catalepsy can be extinguished by repeated exposure to the test environment without injection of haloperidol (FIG. 3). In these experiments rats that showed intensified catalepsy were treated with saline and were repeatedly tested for catalepsy. Under these conditions there was a test-to-test decline (extinction) of catalepsy. Retesting this group (FIG. 3; paired-E group) under haloperidol revealed a small but significant cataleptic response in the paired group, but not in the unpaired group. This shows that intensification was composed of two components: a context-conditioned component that was not expressed when retested under haloperidol and a component that was expressed in the retest with haloperidol (FIG. 3). This latter component

revealed itself in the difference between the response to haloperidol on day 15 and the response to haloperidol observed on the first day of the experiment. This is remarkable since precisely the same results were obtained studying psychostimulant-induced sensitization. Thus, it may be concluded that context-dependent intensification of catalepsy follows the same rules as context-dependent psychostimulant-induced sensitization (Amtage and Schmidt, 2003).

The nature of the latter component (the catalepsy elicited in the retest with haloperidol) is not fully clear. One explanation may be the following: The drug (haloperidol) could have served as an interoceptive cue that had become associated with the context. During extinction tests with saline other contextual cues would have lost their ability to elicit catalepsy but this putative interoceptive cue would not have been extinguished. In the above case, the retest under haloperidol would have produced this interoceptive cue that was associated with the context and elicited the intensified response (FIG. 3).

Emanating from the above considerations, the new view of Parkinson's disease is that a dopamine deficit does not immediately block the execution of behaviour. Rather, it represents an anti-reward signal leading to an extinction-like decline of motor behaviour. This means that mechanisms like those underlying reward-related incentive learning also control motor behaviour.

DYSKINESIA

After about 5 years of L-DOPA treatment, 50% of parkinsonian patients exhibit dyskinetic symptoms consisting of dystonia and involuntary movements. Dyskinesias are very distressing for the patients and represent a most severe side effect of L-DOPA treatment that so far can not be treated adequately. Here only the most frequent form of dyskinesias will be discussed, which are choreic or choreoathetoid in nature and occur at the peak effect of L-DOPA. There are many unresolved issues and the nature of dyskinesias is poorly understood. However, it is well established that dyskinesias only occur in dopamine-denervated states, and that the degree of dopamine loss correlates with the severity of symptoms. Moreover, they mostly appear on the side where parkinsonian symptoms first appeared, *i.e.*, the more denervated side. Also in animal models, the severity of dopamine depletion correlates with the severity of dyskinesias, the stronger the depletion, the earlier the onset and the intensity of dyskinesias.

The mechanisms underlying the development of dyskinesias is not fully understood and a matter of current discussion (Tomiyama *et al.*, 2005). However, some hypotheses posit that the development of dyskinesias represents a form of behavioural sensitization because they develop progressively over time, because in a dyskinetic animal the response to L-DOPA is greater than in a naïve individual and because dyskinesias are inducible by L-DOPA after long periods without L-DOPA - implying an enduring change in neural responsiveness. Graybiel *et al.* (2000) carefully reviewed the literature and made a very strong statement in favour of the similarities between L-DOPA-induced dyskinesias and the sensitization of dopamine-induced stereotypies. Graybiel *et al.* (2000) also pointed out that the relative enhancement of striosome over matrix activation is a predictor of the amount of stereotypy that develops and that striosomes are critical for both reward-related learning leading to sensitization as well as for the development of dyskinesias (Table I).

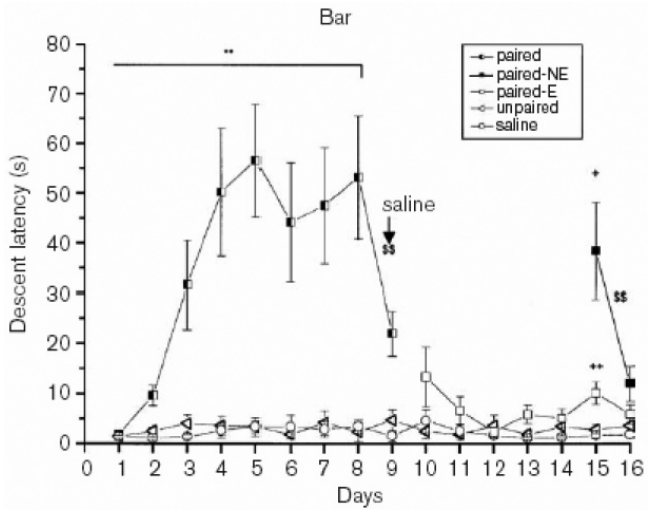

FIGURE 3 Test of classical conditioning through extinction of the haloperidol-induced catalepsy sensitization. The paired group (n=20) was treated for 8 days with haloperidol (0.25 mg/kg) and tested on bar and grid test of catalepsy. Thirty minutes after the test, all animals received saline in their home context. The unpaired control group (n=10) received saline on the first 8 days, 1 h before the test on bar and grid, and 30 min later received haloperidol (0.25 mg/kg) in the home cage. The saline control group received saline on the same time schedule before and after the tests. On day 9, all animals were challenged with saline (CH1 S/S), before and after the test on bar and grid. Half of the paired group (paired-E) was exposed to a 5-day extinction training, where saline was given before and after the test. The remaining half (paired-NE) was not treated or removed from the animal facility during this period of time. Both control groups were treated in the same way as the paired-E group during this time period (from day 10 to day 14). On day 15 all groups were exposed to a haloperidol (0.25 mg/kg) challenge (CH2 H/S), and on the following day to a saline (CH3 S/S) challenge. All data are presented as means ± SEM. Friedman ANOVA for non-parametric data: $^{*}P$ <0.05, $^{**}P$ <0.01 (days 1-8); Mann-Whitney U-test: ^{+}P <0.05, ^{++}P <0.01, comparing the paired-NE group with the paired-E group, and comparing the paired-E group with both control groups; Wilcoxon signed rank test: $^{\$}P$ <0.05, $^{\$\$}P$ <0.01 (days 8-9; 14-16).

Table I

Commonalities between	Sensitization	Dyskinesias
Activation of Dopamine-receptors	+	+
Increased Glutamate transmisssion	+	+
Activation of NMDA receptors	+	+
NR1 and NR2B subunit phosphorylation	+	+
CREB pathway activation	+	+
Activation of Fos, Fra, Jun families	+	+
Prolonged activation of delta Fos B	+	+
Prepro-dynorphin, -enkephalin	+	+
Striosome-over-matrix activation	+	+

modified after Graybiel *et al.,* 2000

In conclusion, the present examples show that sensitization processes may be much more common than previously thought. Pathological dopamine hyperactivity appears to initiate a sensitization process in schizophrenia; drug-induced dopamine hyperactivity plays a role in addiction, in dopamine-induced psychosis and possibly in L-DOPA-induced dyskinesias. Finally, and perhaps most surprisingly, reduced dopamine activity causes a gradual decline not only in rewarded responding but also in general, apparently non-rewarded motor behaviour.

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