韓國心理學會誌 : 生物 및 生理
Korean Journal of Biological and Physiological Psychology
1993.Vol.5, 95-113

Theories of Neuroleptics' Effects on Operant Behavior

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Behavioral Pharmachology has provided more refined animal models for investigating the effects of subcataleptic doses of neuroleptics on operant behavior since the early day of behavioral pharmachology. Based mainly on findings obtained from classical neuroleptics that are either D_1/D_2 mixed antagonists or D_2 antagonists, some theories connected this neuroleptic-induced phenomena to anhedonia (incentive / motivational) changes, whereas others used motor impairments, and associative deficits as explanatory concepts. First, the anhedonia hypothesis assumes that reinforcers have hedonic value for the organism, and this hedonic impact is mediated through dopaminergic neurotransmission as case that mesolimbic DA system is the neuronal circuitry involved in reward/motivational processes. Second, the motor effects hypotheses focused on identification of motor side effects of neuroleptics drugs, in addition to the findings of the behavioral studies, likehood of neuroleptic-induced motor impairment is also suggested by the fact that among the anatomical regions where DA antagonists bind is the striatum which is a part of the extrapyramidal motor system and claimed to be involved in control of motor activity. Third, possible effects of neuroleptics on processes other than motor activities were suggested by the fact that antipsychotics target the mesolimbic and mesocortical DA system, which are believed to be important in memory and learning process. Taken together, re-evaluation of three major hypotheses may helpful to clarity some of the issues related to D_1 and D_2 antagonists and functional roles of respective receptors.

Behavioral pharmacology studies' indicate that effects of both D_1 and D_2 receptor antagonists appear to be effective in disr-upting instrumental behavior. However,this functional similarity is probably mediated through different mechanism; although the end result is response suppression, the way these antagonists exert their effects differ. How this difference translates into associative, this functional similarity is probably mediated through different mechan-ism; although the end result is response suppression, the way these antagonists exe-rt their effects differ. How this difference translates into associative, anhedonia (incentive/motivational), and motor proces-ses involved in ongoing behavior and the clinical relevance of these effects are not clear. Since

the major endeavorhaving clinical relevance is to design neuroleptic drugs with minimal motivational, cognitive, and motor side effects, the importance of the issue is evident. At this point, re-evaluation of three major hypotheses may be helpful to clarify some of the issues related to D_1 and D_2 antagonists and functional roles of respective receptors.

Subcataleptic doses of neuroleptics suppress a variety of instrumental behaviors reinforced by food (Beninger et al.,1987; Clody & Carlton, 1980; Wise et al., 1978), water (Nakajima, 1986), intracranial brain stimulation (ICBS) (Ettenberg et al., 1979, 1981; Fouriezos et al., 1978) and saccharine (Nakajima, 1986). Although this finding was consistently reported in different paradigms such as response rate in Skinner box, running speed in a runway, or place preference in the conditioned place paradi-gm (CPP), theoretical and practical implications of the phenomenon have been subject to debate among investigators. Some theories connected this neuroleptic-induced phenome-na to incentive/motivational changes (Wise, 1982), whereas others used motor impairment (Fowler, 1990), and associative deficits (Salamone, 1992) as explanatory concepts. These theories, while agreeing on a deficit induced by neuroleptic, are divided in term of conceptualizing the factors that account for these observed changes in behavior.

All of these theories are based mainly on findings obtained from classical neuroleptics that are either D_1/D_2 mixed antagonists or D_2 antagonists. However, developments related to D_1 and D_2 receptor antagonists and improvement of specific D_2 receptor antagonists such as raclopride and remoxipride are also thought to have relevance for the suggested processes involved in the behavioral suppression. The-refore, the D_1-D_2 distinction is also integrated into related research and conceptualizations in the context of each theory. This study summaries the differences between these theories, and each hypothesis and the evidence supporting it are discussed. Then, the positions taken in each theory related to the D_1-D_2 distinction and their implications are addressed.

Anhedonia hypothesis.

The incentive/motivational (or anhedonia) hypothesis was originally formulated by Wise and colleagues to explain the suppression of instrumental responses in rats following neuroleptic administration (Fouriezos & Wise, 1976). The anhedonia hypothesis and the notion of neuroleptic-induced reward reduction are based on studies demonstrating that pattern of responding under acute neuroleptic treatment resembles the pattern of responding seen during extinction and/or reward reduction (Fouriezos & Wise, 1976, Fouriezos et al., 1978; Gerber et al.,1981; Wise et al., 1978; Wise, 1982). According to this hypothesis, subcataleptic doses of neuroleptics suppress operant behavior by altering the "hedonic impact" of rewards. Therefore, subjects gradually diminish the behavioral output and quit responding in a way which is similar to response patterns observed during extinction. Thus, the anhedonia hypothesis assumes that reinforcers have hedonic value for the organism, and this hedonic impact is mediated through dopaminergic neurotransmission (Fo-uriezos

et al., 1978). Clark & White (1987) suggested that mesolimbic DA system is the neuronal with DAergic transmission in this circuitry, neuroleptics alter the "hedonic impact" of rewards (Wise, 1982). This major effect of neuroleptic was proposed to be on motivational processes, while motor and perceptive abilities remained intact (Wise, 1982).

Proponents of the anhedonia hypothesis claim that the observed change in responding cannot be accounted for solely by drug elimination or accumulation because control procedures rule out such a possibility (Beninger et al., 1987; Wise et al., 1978). Moreover, the hypothesis claims that since the animals apparently "look and act normal" at the beginning of a given test session, and the effect gradually develops within a session, motor effect cannot account for the observed behavioral change either (Fouriezos et al., 1978; Wise et al., 1978; Wise 1982).

Therefore, the conclusion drawn by the hypothesis is that the animals are capable of responding and of being guided by other environmental stimuli (Gerber et al., 1981), but they do not want to respond because they do not have motivation or incentive to do so due to the blockade of a dopamine mediated reward system in the mesolimbic CNS structures by the central actions of neuroleptic (Wise, 1982). This view claims that neuroleptics have more selective effects than simply inducing deficits in initiating, organizing, or sustaining motor and sensory motor acts (Gerber et al., 1981). Wise and colleagues (1978) claimed that neuroleptic-induced response suppression and the concept of hedonia might be related to schizophrenia and Parkinsonism. Wise et al.(1978) hypothesized that Parkinsonism involved a lack of sensitivity to rewarding stimuli, which was similar to the loss produced by neuroleptics in animals and humans. On the other hand, the affective disturbances in schizophrenia were hypothesized as an overstimulation of such stimuli (Wise et al., 1978).

Although based upon the findings with D_2 and Mixed D_1/D_2 antagonists, the anhedonia hypothesis also addressed the D_1-D_2 receptor distinction and its functional role. However, views on this issue are conflicting. First, Wise (1983) claimed that D_1 antagonism was associated with motor deficits, but D_2 antagonists had an unquestionable effect on reward reduction. Similar views were later advanced by Clark and White (1987). This first position implied that the D_1-D_2 distinction may differentiate between the motivational and motor effects of neuroleptics. Later studies based on the premises of the hypothesis showed that D_1 and D_2 blockers both have performance suppressing effects in heroin (Nakajima & Wise, 1987) and cocaine (Woolverton & Virus, 1989) self-administration; ICBS rei-nforcement (Hunt & Jackson, 1988; Kurumiya & Nakajima, 1988; Nakajima, 1989; Nakajima & Mckenzie, 1986) and food, water and saccharine reinforcement (Beninger et al., 1987; Nakajima, 1986; Nakajima & Baker, 1989; Woolverton & Virus, 1989).

However, observed differences in producing response suppression by D_1 and D_2 blockers attracted much more attention than similarities; therefore, different roles are attributed to functions of D_1 and D_2 receptors in mediating the hedonic value of rewards (Nakajima, 1989). Thus, the way this effect is produced and the importance of D_1 and D_2 receptors in motivational

processes were not clarified within the framework of the anhedonia hypothesis.

Nakajima and Mckenzie (1986) trained their rats to make contact with a metal spout in order to obtain ICBS. SCH23390 (0.01-0.08 mg/kg, ip) reduced the number of spout contacts with an ED_{50} value of 0.022 mg/kg. When the same rats were tested in a runway for ICBS reward, 0.01 mg/kg of SCH23390 produced significant suppression of running speed, and increases in number of ICBS pulses in the goal section of the runway reportedly reversed theeffects of SCH23390 on running speed. In the spout contact task, haloperidol (0.25 mg/kg) completely suppressed responding. 50 mg/kg of sulpride had no effect on running speeds but 100 mg/kg reportedly produced "motor dyscoordination" (Nakajima & Mckenzie, 1986). These researchers concluded that D_1 receptors but not D_2 receptors are involved in mediation of ICBS reward.

Similar results for ICBS were also reported by Kurumiya and Nakajima (1988). These investigators showed that injections of SCH23390 (5 μg or 0.005 mg/kg) into the nucleus accumbens completely suppressed lever pressing for ICBS. The same dose of haloperidol was less effective and sulpride (20μg or 0.02 mg/kg) had no effect at all. Hunt and Jackson (1988) investigated the involvement of D_1 and D_2 receptors on ICBS by using a FI schedule and found that both SCH23390 (5-20 μg/kg or 0.005-0.02 mg/kg, ip) and spiperone (10-50 μg/kg or 0.01 0.05 mg/kg, ip) reduced responding. However, effects of spiperone were reportedly environmental stimuli, whereas SCH23390 was effective in reducing latency to initiate the first movement, but once bar pressing commenced, the proportion of the vigorous responding was similar to the underdruged state.

The anhedonia hypothesis, therefore, emphasized the importance of D_1 receptors as opposed to D_2 receptors in mediation of motivational effects of rewards. At the same time, Gallistel and Davis (1983) claimed that affinity for the D_2 receptor predicts neuroleptic potency in blocking the reinforcing effect of medial forebrain bundle stimulation. Similarly, Clark and White (1987) suggested that the findings from the self-administration and CPP paradigms suggest an important role for D_2 rather than D_1 receptors in the mediation of such processes.

Because of the availability of fast acting and highly specific D_2 receptor antagonists and of the increasing number of studies consistently demonstrating the effects of D_2 antagonists, proponents of the hypothesis changed their position and attributed different roles to D_1 and D_2 receptors in the context of anhedonia hypothesis.

Beninger and coworkers (1987) demonstrated that pimozide (0.5 or 1.0 mg/kg), SCH23390 (0.01, 0.05, 0.10 mg/kg) and metoclopramide (1.0, 5.0, 10.0 mg/kg) resulted in both intra- and intersession declines in responding for food. Nakajima and Baker (1989) found that raclopride (0.02-0.08 mg/kg, ip) suppressed bar pressing for ICBS (ED_{50}=0.079 μmol/kg or 0.039 mg/kg) and food (ED_{50}=0.58 μmol/kg or 0.28 mg/kg). In this study, increases in frequency of ICBS or type of schedule of reinforcement did not alter the effectiveness of raclopride. Reported ED_{50} value for CRF schedule was 0.577 μmol/kg (0.286 mg/kg) and 0.562 μmol/kg (0.279 mg/kg) for VI schedule (Nakajima and Baker, 1989). This study

also demonstrated that SCH23390 showed differences depending on the intensity of ICBS, with higher doses of SCH23390 required to suppress lever pressing for 160 Hz frequency (ED_{50}=0.106 μmol/kg or 0.042 mg/kg) than for 60 Hz frequency (ED_{50}=0.058 μmol/kg or 0.023 mg/kg). Since different doses of raclopride were required to suppressed responding for ICBS and food, Nakajima and Baker (1989) ruled out any kind of motor deficit explanation and suggested that D_2 receptors are related to type of reward. On the other hand, since effectiveness of SCH23390 changed depending upon the intensity of ICBS or the schedule of reinforcement. These authors claimed that D_1 receptors play a role related to efficacy of reinforcement (Nakajima & Baker, 1989).

Nakajima (1989) reviewed the studies related to effects of D_1 and D_2 receptor antagonists and formulated the theory that effects of D_2 antagonists changed depending upon the type of reward being used, whereas D_1 antagonists selectively modify the efficacy of reinforcement. He also proposed that rever- sal effects of SCH23390 by increasing the value ICBS or equipment of high dose of SCH23390 to suppress responding maintained by high pay off schedules ruled out the general motor deficit as an explanation for observed effects. It is suggested, therefore, that D_1 receptors are related to efficacy of reinforcement, whereas D_2 receptors are related to the type of reinforcement (Nakajima, 1989; Nakajima & Baker, 1989). However, some other studies suggested that D_2 antagonism did not always differentiate between type of reinforcers (Nakajima & Baker, 1989; Nakajima, 1989; Woolverton & Virus, 1989; Clody & Carlton, 1980).

Although the anhedonia hypothesis proposed that like D_2 receptors, D_1 receptors are also involved in motivational processes, the similarity of D_1 antagonist-induced response suppression to extinction has not been clarified. Numerous studies demonstrated that SCH23390 is capable of producing response suppression in operant settings; however, whether this suppression increases within a given session is not known. Some studies reported within-session decline induced by SCH23390 (Beninger et al., 1987; Kurumiya & Nakajima, 1988), but others did not address this issue at all (Hunt & Jackson, 1988; Nakajima, 1986) or reported no within-session decrement (Sanger, 1987). It is not clear, therefore, whether the effects of D_1 antagonists on instrumental responding can be explained in the context of the anhedonia hypothesis.

While the anhedonia hypothesis remains one explanation for the effects of DA antagonists on suppression of appetitively motivated instrumental behavior, other studies investigating motor deficits in neuroleptic-induced response suppression questioned the validity of this hypothesis. The anhedonia hypothesis was criticized as being not comprehensive enough to include motor impairments among its explanatory concepts from three lines of research. First, several investigators showed that effects of neuroleptics in operant paradigms and pattern of response suppression are not restricted to appetitively motivated instrumental responses. Sanger (1986) demonstrated that extinction like within-session decrements are observed in both aversively and appetitively motivated operant responding. Sanger (1986) found that D_2 blockers

such as haloperidol and pimozide at doses ranging from 0.01 to 1.0 mg/kg, ip, produced within-session decrements both in food reinforced lever pressing under fixed ratio schedule and in one-way shock avoidance in rats. Similar results were also reported by Acquas et al. (1989) in a conditioned place paradigm (CPP).

Since the anhedonia hypothesis was based on the assumption that appetitive reinforcers has a hedonic value which are blunted by neuroleptics (Wise,1982), it is difficult to explain the findings of both Sanger (1986, 1987) and Acquas et al. (1989) in terms of the anhedonia hypothesis unless the theory attributes some "hedonic values" to electric shock and apparently aversive effects of drugs. Thus, available data suggest that the theory should be modified to explain these observations either in terms of a general motivational state or of another conceptual framework.

The second line of research demonstrated that patterns of neuroleptic-induced response suppression were not as similar to extinction or reward reduction as originally proposed by the anhedonia hypothesis (Faustman & Fowler, 1982; Mason et al., 1980; Spivak & Amit, 1986; Willner et al., 1988; Wirtshafter & Asin, 1985). For example, Mason et al. (1980) claimed that neuroleptic-induced extinction like effects were not seen in every situation. The pattern of behavioral suppression changed depending on the schedule of reinforcement. These researchers demonstrated that within-session decline was not observed in pimozide treated rats responding in a DRL schedule for food although this pattern was observed in another group of rats responding under CRF schedule of the same reinforcer (Mason et al., 1980). Thus, these investigators claimed that extinction like gradual suppression of operant response develops with repeated responses (Mason et al., 1980; Willner et al., 1988). A third line of research further weakened the anhedonia hypothesis by showing the involvement of motor impairment in response reduction induced by subcataleptic doses of neuroleptics as studied in operant paradigms (Ettenberg et al., 1979, 1981; Fowler, 1990). This line of research suggest that behavior itself is a dynamic component of the response reduction.

Motor effect hypothesis.

Instead of emphasizing the effects of neuroleptics on motivational aspects of the behavior in relation to dopaminergic transmission as in the anhedonia hypothesis, the motor effects hypotheses focuses on identification of motor side effects of neuroleptic drugs. In addition to the findings of the behavioral studies, likehood of neuroleptic-induced motor impairment is also suggested by the fact that among the anatomical regions where DA antagonists bind is in the striatum which is a part of the extrapyramidal motor system and claimed to be involved in control of motor activity (Salamone, 1987; Fuxe et al., 1985; Ettenberg, 1989). Studies suggesting the involvement of some type of motor deficit in neuroleptic-induced operant response suppression used this anatomical structure and attempted to draw analogies with of this anatomical site.

Findings pointed to the insufficiency of the anhedonia hypothesis and brought forward several types of motor deficits observed in operant paradigms. On the basis of available data, several variations of the motor impairment hypothesis are available, depending on the natural and circumstance in which the deficit became pronounced.

Some researchers claimed that the neuroleptics increase the latency to respond in different behavioral paradigms (Fibiger et al., 1975; Sanger, 1986; Spivak & Amit, 1986). However, attempts to generalize this finding to neuroleptic-induced response suppression had limited success. For example, Fibiger and Associates (1975) suggested that neuroleptics selectively block the initiation of "voluntary responses" but do not greatly effect reflexive responses. However, originally based upon the findings from CAR studies, this formulation found little ground to explain the response suppression seen in operant studies investigating the effects of neuroleptics on appetitively reinforced behaviors. These studies consistently reported the lack of response initiation problems and pointed out the different types of motor deficits induced by neuroleptics.

Other researchers suggested that neuroleptics produce task dependent effects, and performance on tasks with higher kinetic requirements (i.e. motorically demanding) are more open to neuroleptics' effects than are tasks less difficult (Ettenberg et al., 1979, 1981; Ettenberg, 1989).

Ettenberg et al.(1979) showed that when the response requirements of the same rats were manipulated, the effects of neuroleptics were also differed. Therefore, they claimed that the apparent suppression of reinforced behaviors depended at least in part on the requirements of the response, and tasks relatively harder to perform are more affected by neuroleptics than were easier ones (Ettenberg et al., 1979, 1981; Rolls et al., 1974). However, application of kinetic requirements hypothesis were claimed to be restricted to situations where behaviors with different topographies were required (Fowler & Kirkpatric, 1989; Fowler, 1990). They demonstrated that behaviors having the same topography (i.e. bar pressing) but different kinetic requirements (force bands for reinforcement) were not differentially affected by neuroleptics. In addition, Gramling and Fowler (1985) found that the neuroleptics impaired the operant licking more than reflexive licking. This finding indicated that vulnerability of a response to the effects of neuroleptics was not completely determined by its kinetic aspects.

Although their theoretical approach with regard to the neuroleptic-induced response sup pression could not be applied to many situations, an important point raised by these authors was that repetitive responding was an important component of gradual within-session decline, resembling extinction in drug-free conditions (Ettenberg et al., 1979; Mason et al., 1980; Rolls et al., 1974). These studies mentioned above collectively emphasizing that neuroleptic-induced motor impairment is involved in response suppression and this involvement cannot be explained in terms of anhedonia hypothesis or of an impaired general motivational state so that at least some type of motor impairment should be included as an explanatory concept. Findings supported the motor impairment notion showing that neuroleptics such as haloperidol and pimozide induced lengthening of response duration which precedes and accompanies rate decline. This effect of neuroleptics gradually increased with repeated responding until the subject abruptly stop responding (Ettenberg, 1989). Thus, neuroleptics induce changes in the temporal properties (i.e. timing) of discrete responses showing themselves as slowing response termination. This response pattern induced by neuroleptics was suggested to be analogous to Parkinsonian slowing of individual responses, impairment of rapid altering movements, and abrupt cessation of responding in

humans (Ettenberg, 1989).

The physiological mechanism offered for the behavioral process involved a depletion of striatal presynaptic DA produced by responding which is simultaneously accompanied by already depleted presynaptic DA resulting from neuroleptic-induced increases in DA turnover and relatively high but surmountable postsynaptic DA blockade (Fowler, 1990). According to this hypothesis, the short-term increase in DA availability provided by increased DA turnover in the early phase of a session is sufficient to override temporarily the blockade of the postsynaptic DA receptors.

Therefore, the level of DA occupied receptors rises above a critical threshold for movement expression. However, since the post- synaptic DA is already depleted, this activation effect is short lived, while DA release declines and available DA is used up by repeated behavior, behavioral outcome also declines accordingly. Later, receptor occupancy by DA sufficiently drops below the threshold for response expression, and behavior abruptly ceases. This formulation is mainly based on several assumptions, some of which have important implications in relation to the prediction of possible motor effects of D_1 antagonists: 1) DA release in the striatum is increased by acute administration of classical neuroleptics; 2) there exists a DA receptor occupancy threshold for response expression; and 3) etiological and behavioral analogies to parkinsonism combined with attenuating effects of anticholinergic drugs imply that changes in temporal parameters of the response and resulting within-session decline are mediated by striatal DA depletion and increased ACh release.

Although the hypothesis was comprehensive and provided testable predictions, the D_1-D_2 receptor distinction has not been tested in context of this hypothesis and further research addressing this issue may reveal the differences between D_1 and D_2 antagonists in terms of their parkinson like effects. Another important point which can be raised about the hypothesis is that although strong analogies to behavioral effects and etiology of Parkinson's disease were established, the theory is mainly based on force-time measurements from the learned forelimb responses of rats. Therefore, this version of the motor effects hypothesis requires testing of D_1 and D_2 antagonists in paradigms specifically investigating the changes in temporal parameters of more complex responses.

Associative effects hypothesis

Possible effects of neuroleptics on processes other than motor activities were suggested by the fact that antipsychotics target the mesolimbic and mesocortical DA systems, which are believed to be important in memory and learning processes. Some studies indicated that in addition to their motor effects, neuroleptics influence learning and memory processes (Clody & Carlton, 1980; Levin et al., 1987; Ljunberg Enquist, 1990). Interpretation of these findings differed markedly depending on the paradigm being used. For example, Clody and Carlton (1980) showed that chlorpromazine-induced effects can be attenuated by increases in stimulus efficacy (i.e. responding controlled by the more efficacious stimuli was consistently less affected). Therefore, these authors suggested that neuroleptics impair stimulus-response associations. Similarly, it is also possible to evaluate the findings reported by Acquas et al. (1989) in conditioned place preference

(CPP) paradigm in the same context. Since CPP paradigm is based on the approach to or avoidance from stimulus paired with positive or negative reinforcers, blockade of both types of behaviors can be evaluated within the framework of loss or weakening of established associations during the training.

Furthermore, CAR studies might have the same implication suggesting that shifts from nonsignaled periods to signaled and shock periods might be the result of loss of stimulus efficacy (Clody & Carlton, 1980).

Whereas some researchers focuse on stimulus efficacy, others demonstrated that the effects of neuroleptics on learning and memory are not solely limited to stimulus associations. Levin and coworkers (1987) demonstrated that haloperidol results in choice accuracy deficits in rats in a radial arm maze, and they inferred cognitive deficit similar to the one seen in Parkinson's disease patients. Levin (1988) later reported similar findings with raclopride (5 mg/kg, ip); but SCH23390 (0.1 mg/kg) reportedly did not induce such an effect.

Whishaw et al. (1989) also showed that learned behavior itself is an important target of the neuroleptic effects. These authors demonstrated that treatment with alpha-flupentixol gradually increased the latencies to initiate swimming behavior in a swimming pool task in which rats had to find and climb on top of a small platform located in the water. Thus, these researchers proposed that experience with the learned component of the task is essential for maximizing the disrupting effects, and that the observed decay in performance was not simply due to motor impairment but depended upon experiencing relevant task contingencies.

An important issue raised by Whishaw and coworkers (1989) may have significant implications in terms of organizing the results of the studies mentioned above as well as making predictions about neuroleptic effects on learned behavior that have clinical and theoretical significance. They suggested that behavior may be organized in subsystems, and each subsystem and the learned connections between them may be differentially sensitive to neuroleptic actinon.

This idea was supported by another study addressing the D_1 and D_2 receptor involvement in organizing two behavioral options (locomotion and bar pressing) to maximize reward (Ljunberg & Enquist, 1990). In this experiment rats had to press a lever in order to obtain water. However, lever pressing might also turn off the lever with a probability of 0.1. When this happened, further lever presses did not result in delivery of reward. After detecting invariability of reward by a number of non-rewarded-lever-presses, the subject had to turn the lever on by executing another learned behavior that consisted of interruption of a photobeam located in a remote session of the apparatus. Breaking the photobeam resulted in immediate delivery of the reward and turned on the lever which was programmed to deliver the reward with a probability of 0.9 after each lever press. When the lever was off, control rats made several successive lever presses, then ran to the photobeam. However, haloperidol (0.02-0.1 mg/kg, sc) did not only result in a dose dependent decrease in total number of rewards but also impaired the rat's ability to turn the lever on by breaking the photobeam. Ljunberg and Enquist (1990) reported that the latter type of impairment largely resulted from lever presses with higher IRTs when the lever was off and delayed breakage of the photobeam after the last lever press in a non-reward condition. The same kind of

behavioral patterns were observed in three other groups after SCH23390 (0.01-0.05 mg/kg, sc) administration. However, the highest dose of SCH23390 reportedly resulted in very low and variable performance that could not be tested for significance.

Ljunberg and Enquist (1990) concluded that neither haloperidol nor SCH23390 result in deficits in "information sampling" as assessed by the number of lever presses in a lever off situation. These authors also suggested that both the kinetic requirement hypothesis and the anhedonia hypothesis could not explain the deficits observed as failures of organizing two behavioral options into a functional sequence. Ljunberg and Enquist (1990) explained the deficits observed in their paradigm in terms of neuroleptics' effect on "initiation and / or performance of a given behavior in a learned task" and claimed that rather than producing a single effect on performance, neuroleptics induce a more general type of deficit characterized by impairments of use of motor acts in complex contexts.

Results of this study had important implications. First, as also implied by Whishaw et al. (1989), data from Ljunberg and Enquist (1990) suggests that in a learned task, although the individual motor acts may remain relatively intact, organization of these acts into a functional sequence may be selectively disrupted by neuroleptics. The second implication is that not only D_2 antagonists but also D_1 antagonists are capable of producing such a deficit, and data suggests that SCH23390 is more potent than haloperidol in this respect. Therefore, behavioral research investigating the effects of D_1 antagonists in single motor acts such as catalepsy may not be able to provide a reliable assessment of potential side effects of these compounds. Finally, even though anticholinergics may partially reverse neuroleptic-induced impairment individual motor acts, neuroleptic-induced deficits in the use of different motor acts as functional components in the execution of a goal oriented behavioral sequence may not be alleviated. Recent findings reported by Skjoldager and Fowler (1991) also strengthen this argument with demonstration that haloperidol (0.04-0.06 mg/kg, ip) produced attentional and motor disturbances in a sustained attention task. While coadminstration of scopolamine (0.02 mg/kg, sc) with different doses of haloperidol reversed the motor effects of haloperidol, the haloperidol induced attentional disturbances were not affected.

These findings, if they can be taken as analogous to Parkinsonism in humans, have important implications in terms of the anticholinergic drug intervention. Although the motor effects of neuroleptics can be alleviated, these drugs do not reverse organizational and attentional (i.e. cognitive) effects of neuroleptics. Therefore, findings of these kind also direct attentions into another type of potential side effect of DA blockade which might have been ignored for a long time. In addition to its clinically relevant implications, another immediate significance of these findings is that neuroleptics will probably produce more pronounced impairment of performance in tasks requiring programming and sequencing different behavioral activities in a behavioral chain because the effects of neuroleptics will probably be observed as both motor and cognitive deficits. The possibility of such a task-neuroleptic interaction was also hypothesized in a different but related context by Cohen and Servan-Schreiber (1992). According to these authors the goal oriented tasks relying on internal representation of context (i.e. cognitive

parameters such as memory) will be differently affected by neuroleptics than tasks involving a set of routine-repetitive responses.

A recent attempt to organize the findings of research on neuroleptics' effects on operant behavior on the basis of associative processes was made by Salamone (1991, 1992). According to this formulation, neocortex and limbic areas are involved in associative, sensory, and affective processes, and DA in the striatum and nucleus accumbens modulates the ability of these processes to influence complex motor functions. The deficits produced by interference with the central DA systems, especially with the striatum and nucleus accumbens, are selective and associative in nature; therefore they affect some features of motor and motivational function but leave others of mainly intact. In other words, although neuroleptics may have diminishing effects on associative, motivational, and motor processes, what is selectively disrupted is the complex learned behaviors having strong associations with conditional stimuli.

According to this model, the proposed role of the striatum and nucleus accumbens is not only a mediator of the execution of complex behaviors but a provider of feedback to the cortex so as enable specific cortical cells to maintain their goal-directed activity and thereby sustain a complex learned pattern of motor behavior. Thus blockade of dopamine receptors in the basal ganglia produces a deficit in this feedback loop and produces a "subcortical apraxia" (Salamone, 1991, 1992). Such a model is helpful to organize the available data in the literature and to introduce new research questions. First, this approach accepts that learning experience is a dynamic determinant of the extent of behavioral disruption that is induced by neuroleptics. For example, this feature of the model can explain the data provided by Rolls et al. (1974) and Ettenberg et al. (1979). Research showing that haloperidol (Wirtshafter & Asin, 1985) and pimozide (Spivak & Amit, 1986) produce differential effects depending on the area run away in relation to start and goal box segments can be explained in the same context because cues that are distal in terms of time and place will require more learning to acquire their effects as discriminative stimuli. Therefore, behaviors sustained by these stimuli will be disrupted first. Secondly, in this model relevant task contingencies are important. Therefore, it is expected that complex tasks with multiple behavioral components that require extensive training will be disrupted more by the neuroleptics. It is possible to explain the findings of Ljunberg and Enquist (1990) and substantiate the claims of Cohen and Servan-Schereiber (1992) in this context. However, the reported effects of extensive training on attenuating neuroleptics' effect in CAR test (Fibiger et al., 1975) may be related to strengthening of sensorimotor cues so that the behavior becomes ballistic and is controlled mainly by subcortical structures such as the cerebellum. Third, the "subcortical apraxia" view minimizes the difference between appetitively and aversively motivated behaviors in neuroleptic research. Therefore, it resolves the debate about why the neuroleptics suppresses both aversively and appetitively motivated behaviors as shown by Sanger (1986, 1987) or Acquas et al. (1989). Fourth, it becomes easier to understand why the anti- cholinergic drugs do not reverse the effects of DA antagonists in certain behavioral tasks. Since the major function of the anticholinergic cotreatment is to alleviate the effects of neuroleptics in the striatum, this type of intervention may produce partial recovery of motor performance

from the effects of neuro-leptics. On the other hand, it is known that receptor-specific drugs such as raclopride and SCH23390 are more active in blocking the limbic structures, one of which is the nucleus accumbens. One proposed role of the nucleus accumbens is to organize the complex behaviors (Salamone, 1992). The effects of neuroleptics on mesolimbic DA receptors are known not to be sensitive to anticholinergic challenge (Nielsen, 1988). If the behavior is complex in a sense that consists of multiple motor components each of which require extensive training and more involvement of the nucleus accumbens in its organization and planning, then the D_1 and/or D_2 antagonist induced deficits will be more complicated. Therefore, in this case, anticholinergic intervention targeting the striatal deficit may not be enough to reverse the effects of D_1 and D_2 antagonists. Interestingly, some findings imply that anti-cholinergic cotreatment does not reverse the effect of D_2 antagonists in tasks which can not be solely defined as motor tasks (Ljunberg & Enquist, 1990) and even worsens the effect of the D_1 antagonist SCH23390 (Iorio et al., 1991).

In addition, although it is not explicitly stated by Salamone (1991, 1992), his model of neuroleptic action may also explain the functional differences of D_1 and D_2 receptor antagonists as studied in aversively and appetitively motivated operant paradigms. The functional role of D_1 receptor type in associative/cognitive tasks were also usually ignored except in a small number of studies (e.g. Levin, 1988; Ljunberg & Enquist, 1990). Although a difference between raclopride and SCH23390 was reported in this context, the role of D_1-D_2 receptor distinction was not explicitly addressed. Therefore, the role of D_1-D_2 receptor distinction awaits further research on this issue. Currently, there is little evidence that D_1 receptor antagonists result in associative or organizational deficits as suggested by Salamone (1992). However, in addition to reports from Ljunberg and Enquist (1990), a recent study by Sawaguchi and Goldman-Rakic (1991) demonstrated that local injections of D_1 antagonists SCH23390 or SCH39166 into prefrontal cortex of rhesus monkeys induced errors and increased latency in memory guided oculomotor saccades without disturbing visually guided saccades is in direct conflict with any notion which claims that organization of complex behaviors can be solely attributed to D_2 receptors.

Reports by Levin (1988) on choice accuracy score of rats in a radial arm maze also indicated SCH23390 (0.10 mg/kg, ip) induced deficits did not differ from those of saline control rats, whereas raclopride (5 mg/kg) induced significant impairments. This result implies that a possible major effect of D_1 antagonism may be disabling the initiation of patterned activity of cortical cells so that the brain's specifications of to be performed acts are not easily made in the first place. In turn, this type of deficit in the cortical activity may result in problems in initiation of the complex behavioral pattern as reported by Hunt and Jackson (1988). On the other hand, if the cortical cells are activated and the motor capacities of the subject are relatively intact, then the effect of neuroleptics may not suppress the subject's behavior to a large extent. This formulation can also explain why D_1 antagonist induced response suppression appears to

be sensitive to the parameters of reinforcement because any detectable change in the parameters of reward will have some effect in the regulation of activational aspects of the cortical cells.

Although this postulation is stimulating, and it provides a conceptual framework in which some of the findings summarized above could be explained, it does not specifically address the issues related to D_1-D_2 distinction and to intact aspects of the associative, sensory, motivational, and motor components of the complex behavior is not clear in this formulation.

Conclusion and Prospect

Re-evaluation of three major hypotheses explained above may be helpful to clarify some of the issues related to D_1 and D_2 antagonists and functional roles of respective receptors. Even if one puts aside the many studies demonstrating that anhedonia hypothesis is not sufficient to explain the response suppression observed following neuroleptic administration, the hypothesis is not strong enough to account for the differences between the effects of D_1 and D_2 antagonists within its own theoretical framework. Motivational roles of D_1 and D_2 distinction as evaluated within the framework of anhedonia hypothesis has not shown consistent development and results are conflicting. The first theoretical commentaries on D_1 receptors was that they might be involved in motor deficits, whereas D_2 receptors were believed to be modulating motivational effects (Wise, 1983). Later studies then suggested that D_1 receptors mediate reward and previously observed effects of D_2 antagonists were attributed to their possible effects on D_1 receptors (Nakajima, 1986; Nakajima & Mckenzie, 1986). The most recent position of the anhedonia theory holds that D_1 receptors are related to the efficacy of rewards whereas D_2 receptors are associated with the type of reward (Nakajima, 1989). However, at least two studies indicate that these postulated functional roles for D_1 and D_2 receptors does not hold (Fibiger et al.,1976; Woolverton & Virus, 1989). Moreover, receptor on whether D_1 antagonists produce within-session decrement or not are also conflicting (e.g. Kurumiya & Nakajima, 1988; Sanger, 1987). Therefore, although the studies mentioned above demonstrated that like D_2 antagonist, D_2 antagonists also induce suppression of appetitively reinforced behavior. This suppression produced extinction like effects are not clear.

However, findings of some of the studies in context of the anhedonia hypothesis might be helpful to identify some characteristics of D1 receptor antagonists. One of these which is important in context of motor and associative effects hypothesis is that repeated responding under D_1 antagonists appears to make subjects more resistant to drug effects. One implication of this finding is that antagonists were not affected or affected in an opposite fashion by repeated responding which is suggested to be a key for within-session decrements in context of motor effects of neuroleptics (Ettenberg et al., 1979, Fowler, 1990; Rolls et al.,1974).

Although the motor effects hypothesis with its strong analogies to human Parkinsonism provides

testable predictions in animal models which might help in identifying the differences and similarities induced by D_1 and D_2 antagonists according to multiple criterion (e.g, temporal changes, interactions with anticholinergic drugs), the hypothesis, as in its current form, is mainly based on the data from response duration and force measurements of rat forelimb. However, considering that effects of neuroleptics on more complex behaviors might show differences from those on repetitive response of rat forelimb, the premises of the hypothesis need to be tested in different paradigms.

When the behavioral observations cited in the preceding paragraph are combined with biochemical and pharmacological data, it can be argued that D_1 and D_2 antagonists will have different effects in terms of their motor effects, and effects of D_1 antagonists will be less likely to resemble the D_2 antagonist-induced pseudoparkinsonism as suggested by Fowler (1990). Therefore, differences are also expected in terms of changes in temporal parameters of behavior and effects of anticholinergic intervention. As stated before, except for the report by Iorio et al. (1991), no anticholinergic challenge of SCH23390 in an operant paradigm has yet been published; therefore, how the appetitively motivated behavior may react to anticholinergic treatment following a D_1 antagonist is not known.

In terms of associative effects hypothesis, research suggest that D_1 and D_2 antagonists are effective in disrupting memory, associations, and attention and organization of behavioral activities in a functional order. A task-drug interaction is implied in the context of the associative effects hypothesis. One difference which may separate associative effects from the motor effects might be sensitivity to anticholinergic challenge of antagonists effects of neuroleptics. However, the data on this issue are limited and role of D_1 antagonists' effects in the context of associative effects hypothesis is not clear.

Given the possibility that the same neural circuits are involved in the mediation of complex behaviors and that the lack of experimental methodology to address these issues separately, it may never be possible to differentiate these process completely. However, predictions of these hypotheses can be tested in experimental designs involving sensitive measures of D_1- and D_2-antagonist-induced effects. In this respect, the analogies constructed between Parkinsonism and neuroleptic effects in motor, cognitive and motivational aspects of behavior in rats in operant paradigms may provide an important direction to follow. Currently, these trends appear to be following different courses by either emphasizing the motor effects in highly elaborated response measures such as force and duration in repetitive responses or by focusing on tasks explicitly designed to measure the effects of neuroleptics in information processing, memory and organization of complex responses. However, considering that motor and cognitive and probably motivational processes are affected by neuroleptics all together, it seems to be possible to include these processes in behavioral methodologies in order to reach a better understanding of D_1 and D_2 antagonists in their side effect profiles though preclinical research.

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Theories of Neuroleptics' Effects on Operant Behavior

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韓國心理學會誌 : 生物 및 生理
Korean Journal of Biological and Physiological Psychology
1993.Vol.5, 95-113

조작 행동에 있어서 신경마비제 효과에 관한 이론들

정 평 수

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행동 약물학(Behavioral Pharmachology)은 잘 통제된 동물 모델을 토대로 항정신성 약물(antipsychotic drug)과 관련된 신경마비제(neuroleptics)의 급작성 복용효과(subcataleptic dose effect) 연구에 크게 기여하고 있다. 이 연구들은 주로 D_1, D_2, 또는 혼합된 D_1/D_2의 길항제 [Antagonists : SCH23390 (D_1), Raclopride (D_2), Pimozide (D_2), Sulpiride (D_2), Haloperidol (D_1/D_2), Thioridazine (D_1/D_2) etc.] 들을 사용한 고전적 신경마비제(classical neuroleptics) 연구로부터 도출된 결과들을 토대로 하여 연구가 진행되고 있다. 이와 관련하여 제기된 신경마비제의 효과에 대한 세 가설을 설명하고자 한다. 첫째로 앤헤도니아 가설 (anhedonia hypothesis)은 신경마비제가 유기체에게 유인가/동기적 가치(incentive/ moti- vational value)를 지니게 됨으로써 이 헤도닉 강화물(hedonic reinforcement)은 신경전달 물질을 매개로 하여 중변연 도파민 기제(mesolimbic dopamine system)에 영향을 미친다는 것이다. 둘째는 운동효과 가설(motor effect hypotheses)로, 신경마비제가 특정 운동기제(specific motor system)에 손상을 야기함으로써 생리적, 기능적으로 부작용(side effect)을 나타낸다는 것이며, 마지막 가설은 연합효과 가설(associative effect hypothesis)로서 항정신제가 기억과 학습에 중요한 중추기관으로 생각되는 중변연(mesolimbic)과 중피질(mesocortical)에 중요한 역할을 한다는 것이다. 결과적으로 이 세 가설을 종합해 볼 때, D_1 과 D_2 길항제와 각 수용기의 기능적 역할들과 관련하여 제기된 문제들을 명확히 하는 데 일조할 것으로 사료된다.