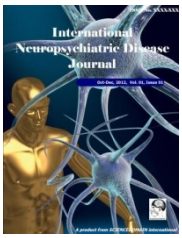

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Interleukin-2 Treatment Induces an Acquired Behavioral Response Pattern (Repetitive Stereotyped Movements) Mediated by Dopamine D1 and D2 Receptors

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Authors' contributions

This work was carried out in collaboration between both authors. Authors ASP and SSZ designed the study and wrote the protocol. Author ASP preformed the statistical analysis, managed the literature search and wrote the first draft of the manuscript with assistance from author SSZ. Both authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Interleukin (IL)-2 is implicated in the etiology of psychiatric disorders (e.g., schizophrenia, psychosis) involving an increased expression of repetitive stereotyped movements. However, little is known about the underlying pharmacological mechanisms or behavioral processes. Of further importance, we sought to identify underlying pharmacological mechanisms. We found that dopamine D1 receptors underlie the development of IL-2-induced stereotypic movements while D1 and D2 receptors are required for the expression of IL-2-induced stereotypies. These findings raised the intriguing possibility that IL-2 treatment induced an acquired behavioral response pattern requiring concurrent stimulation of D1 and D2 receptors. Thus, we determined whether stimulation of D1 and D2 receptors following termination of IL-2 treatment would re-instate the expression of repetitive stereotyped movements (i.e., an acquired response pattern). Based on these findings, we suggest that sub-chronic or chronic elevations in peripheral IL-2 levels may produce behavioral disturbances that persist beyond the presence of IL-2 by altering dopamine receptor activity resulting in the acquisition of an abnormal response pattern, and thus increase vulnerability to psychopathological outcomes associated with repetitive

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stereotyped movements. To our knowledge, these are the first data to identify a process by which a cytokine produces an abnormal response pattern.

Keywords: Interleukin-2; dopamine receptor; acquired behavioral response; stereotyped movements.

1. INTRODUCTION

Interleukin-2 (IL-2) is a T helper (Th1)-derived cytokine that potently modulates activity in the mesostriatal and mesolimbic systems. For example, IL-2 promotes the survival of dopaminergic cells during neurodevelopment, influences spontaneous and evoked dopamine release in vitro [1-3] and modulates NMDA- and kainate-activated currents in dopaminergic cells freshly isolated from the ventral tegmental area (VTA) [4]. In adult rodents, single systemic injections of IL-2 modulate dopamine activity in the medial prefrontal cortex, nucleus accumbens and hypothalamus [5-7]. In parallel, single systemic injections of IL-2 induce locomotion and exploration [3,8-10] while microinjections of IL-2 into nigrostriatal sites induce rotational behavior and asymmetric body posture [11]. IL-2-induced variations in motor activity are related to the chronicity of its administration in that repeated but not single injections induce climbing, which is a repetitive stereotyped movement. IL-2-induced stereotypic behavior was attenuated in mice treated with dopamine D1 or D2 receptor antagonists [12]. A limitation of that study, however, is that mice received home-cage injections of IL-2 and were tested only after the last injection. Thus, the extent to which the development and expression of this effect was mediated by dopamine receptors remains to be determined. While little is known about the relationship between IL-2, behavior, and dopaminergic receptors, there is evidence that chronic IL-2 treatment influences D1/D2 receptor expression in rat striatum and cortex [13]. Furthermore, in patients, concurrent increase in IL-2 and expression of psychotic symptoms were attenuated by treatment with haloperidol, a mixed and Dl/D2 receptor antagonist [14]. In such a process, a stimulus induces a behavioral response and following withdrawal the expression of the behavioral response may be re-instated by stimulation of the underlying neural substrates. It is thus of present interest that Saka and colleagues showed that repeated injections of cocaine induce repetitive motor stereotypies that require concurrent stimulation of dopamine D1 and D2 receptors and that following termination of treatment, stimulation of D1 and D2 receptors produced the acquired behavioral response pattern [15].

In the present study, we thus sought to determine whether dopamine D1 and/or D2 receptors are required for the development and expression of IL-2-induced stereotypic behavior and whether IL-2 treatment results in an acquired behavioral response pattern mediated by dopaminergic receptors. An IL-2-induced acquired response pattern would represent a novel process by which IL-2 (and perhaps other cytokines) proactively influence behavior. Findings could help shed light on mechanisms by which IL-2 may come to induce psychopathological outcomes. Given IL-2's short-half life, it would also seem necessary to show that IL-2 treatment has long-term repercussions on the expression of stereotypic behavior that persist beyond termination of treatment. A powerful way in which a drug may proactively affect behavior following termination of treatment is by inducing an acquired behavioral response pattern.

2. MATERIALS AND METHODS

2.1 Subjects

Adult male BALB/c mice were used in the present study. This strain was selected based on our findings that IL-2 induces marked neurochemical and behavioral changes in BALB/c mice. The mice were obtained from Charles River (Wilmington, MA, USA) at 5-week of age in weight range of 20-25gms and housed in standard polypropylene 'shoebox' cages. The animals were housed in groups of four prior to being used as experimental subjects whereupon they were housed individually. The animals were maintained on a 12-hour light–12-hour dark cycle (7am-7pm) and permitted ad lib access to standard laboratory chow and water. Experiments were conducted during the animal's light phase. The animals were tested 1 week after arrival to the institute. At the end of testing, the mice were euthanized by CO_2. All experiments and procedures were approved by the Institutional Animal Care and Use Committee (IACUC) of the New Jersey Medical School.

2.2 Drugs

Recombinant, murine, and carrier-free IL-2 was purchased from Pepro Tech, Rocky Hill, NJ, USA. SCH 23390 a selective dopamine D-1 receptor antagonist, Sulpiride [a selective dopamine D-2 receptor antagonist], SKF 81297 a selective Dopamine D-1 receptor agonist] and Quinpirole a selective Dopamine D-2 receptor agonist were purchased from Tocris Cookson, Ballwin, MO, USA. All drugs were dissolved in sterile saline solution and final volume of injectable solutions were maintained to be 0.2ml/drug for each experiments.

2.3 Statistics

Data were analyzed using one-way analysis of variance (ANOVA) using Graph Pad software. Bonferroni post-hoc tests ($\alpha = 0.05$) were used to confirm group differences. For each experiment, mice in control groups were compared with mice in treatment group for behavioral differences. Treatment groups were compared with control groups only in experiments involving dose determinations. Behavioral data either more or less than 2SD than mean were excluded from analysis to maintain statistical analysis structure.

2.4 Experimental Methods

We tested IL-2 induced behavioral changes in presence of dopamine receptor agonist and antagonist to determine role of these receptors in IL-2 related effects.

2.4.1 Effects of dopamine receptors on development and expression of IL-2 induced stereotypy

To identify role of dopamine receptor in development of IL-2 induced stereotypy, the mice were administered either saline or SCH 23390 (0.0125, 0.05 or 0.2 mg/kg) as pretreatment [3,12]. After 15 mins, each mouse received single one time injection of IL-2 (0.4μg) i.p. Immediately following IL-2 injection the mice were individually placed into a shoebox cage containing bedding material for 2 hrs for behavioral observations. The test session were taped with a VHS camera. Same strategy was repeated for 2 additional consecutive days, totaling it to be 3 days experiment. VHS tapes were scored at a later date by an experienced rater for rearing, climbing, sniffing and grooming.

We used same experimental design to study effect of D2 antagonist (Sulpiride) and combined D1 and D2 antagonist (combination of SCH 23390 and Sulpiride).

To identify role of dopamine receptor in expression of IL-2 induced stereotypy, the mice were administered single one time injection of IL-2 (0.4μg) i.p.once a day for 3 consecutive days. On day-4, 15-mins prior to IL-2 injection, mice were administered single injection one time dose of either saline, SCH 23390, Sulpiride or combination of SCH + Sulpiride. Immediately following IL-2 injection the mice were individually placed into a shoebox cage containing bedding material for 2 hrs for behavioral observations. The test session were taped with a VHS camera. VHS tapes were scored at a later date by an experienced rater for rearing, climbing, sniffing and grooming.

2.4.2 Effects of dopamine receptors on IL-2 induced acquired behavioral response

To determine IL-2 induced stereotypy required concurrent activation of D1 and D2 receptor, the mice received single injection of IL-2 (0.4μg i.p) once a day for 3 consecutive days, Immediately after injection, animals were put into shoebox cage for 2 hrs each day. One day following the last IL-2 injection (Day 4 of experiment), the mice were divided into groups receiving a single injection of either Saline or SKF 81297 (1mg/kg i.p.). The test sessions were taped with VHS camera for 2 hours and scored at a later date by an experience rater for rearing, climbing, sniffing and grooming.

We used same experimental design to study effect of Quinpirole (D2 agonist) and combination of SKF 81297 and Quinpirole.

3. RESULTS

3.1 Effects of Dopamine Receptor Antagonist on Development of IL-2 Induced Behavioral Changes

When mice were treated with either (Saline + IL-2) or (SCH 23390 + IL-2) for 3 days, SCH pretreated mice showed reduced amount of time involved in climbing activity Fig. 1A and 1B ($f(1, 35) = 4.97$, $P<0.05$, n= 18/group) and also reduced attempt to climb Fig. 1C ($f(1, 35) = 4.29$, $P<0.05$, n=18/group).

In experiments where mice were treated with either (Saline+IL-2) or (Sulpiride+IL-2) for 3 days, Sulpiride pretreated mice showed reduced amount of time involved in climbing activity Fig. 2A and 2B ($f(3, 30) = 3.45$, $P<0.03$, n=9/group) and also as reduced attempt to climb Fig. 2C ($f(3, 30) = 2.8$, $P<0.05$, n=9/group).

3.2 Effects of Dopamine Receptor Antagonist on Expression of IL-2 Induced Behavioral Changes

When mice were treated with IL-2 for 3 days followed by either saline or combination of SCH 23390 and Sulpiride on Day-4, treatment mice showed reduced attempt to climb on the ledge Fig. 3A ($f(1, 10) = 7.71$, $P<0.02$, n=6/group) as well as reduced time to involve in climbing activity Fig. 3B ($f(1, 10) = 6.03$, $P<0.04$, n=6/group) as compared to control mice. However, when mice were treated with IL-2 for 3days followed by either SCH or Sulpiride on Day-4, no significant changes in behaviors were observed (data not shown).

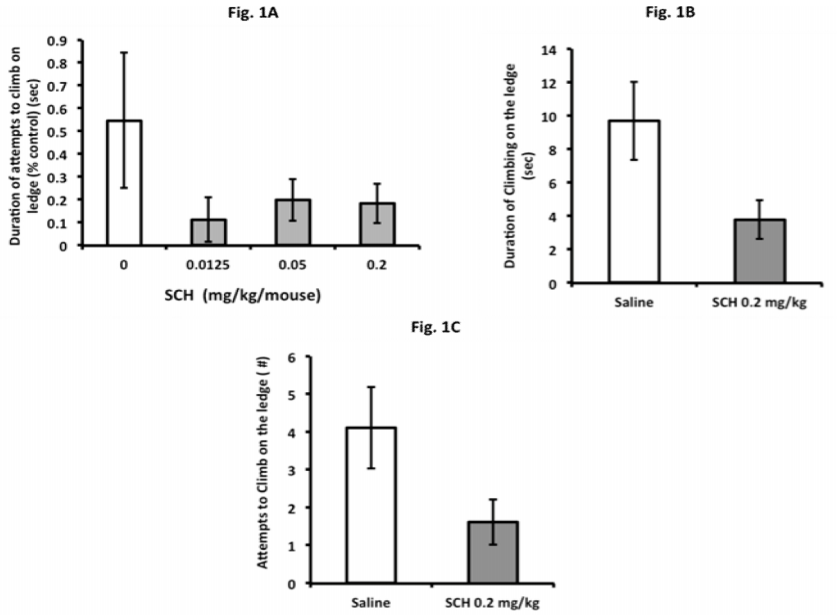

Fig. 1. Effects of SCH pretreatment on IL-2 treated mice. (1A) shows dose response experiments to determine optimal dose for experiments. (1B) shows effect of SCH pretreatment on duration of climbing on the ledge. (1C) shows effects of SCH pretreatment on attempts to climb on the ledge

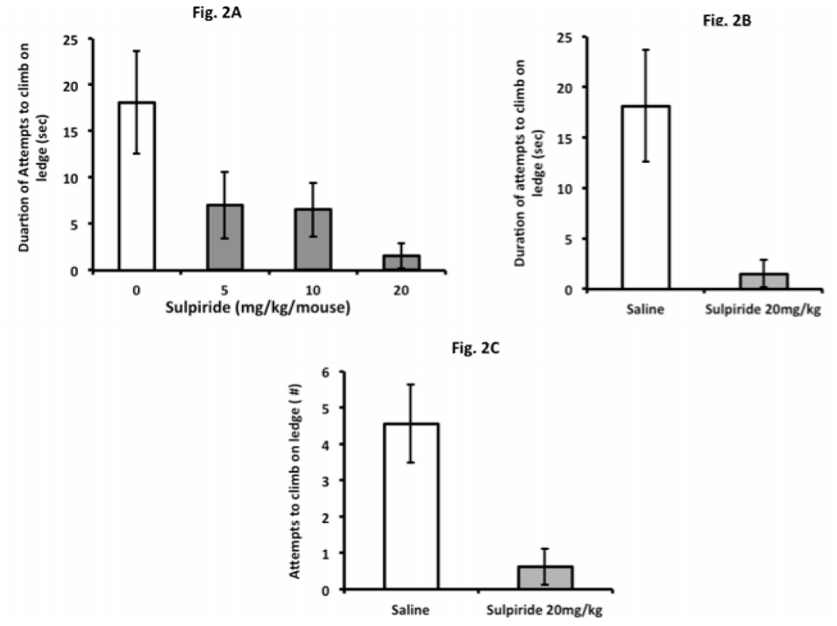

Fig. 2. Effects of Sulpiride pretreatment on IL-2 treated mice. (2A) shows dose response experiments to determine optimal dose for experiments. (2B) shows effect of Sulpiride pretreatment on duration of climbing on the ledge. (2C) shows effects of Sulpiride pretreatment on attempts to climb on the ledge

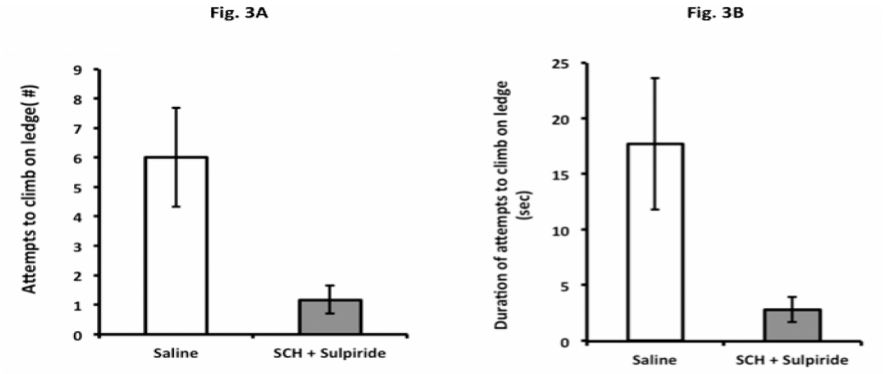

Fig. 3. Effects of SCH+Sulpiride on expression of IL-2 induced activity. (3A) shows significant effect of SCH+Sulpiride on attempts to climb on the ledge. (3B) shows significant effects of SCH+Sulpiride on duration of climbing on the ledge

3.3 Role of D-1 and D-2 Agonist on IL-2 Induced Acquired Behavioral Response pattern

We showed that dopamine receptors are involved in development and also expression of IL-2 mediated effects. We also studied mice after repeated IL-2 administration to show whether administration of dopamine receptor agonist would enhance IL-2 effects. Mice were treated with IL-2 for 3 days following same experimental method mentioned earlier. On Day-4, mice were treated with either saline or combination of SKF 81297 and Quinpirole. Dopamine agonists treated mice showed increase attempt to climb on the ledge Fig. 4A ($f(1,13) = 4.72$, $P<0.05$, n=8/group) as well as increased time to involve in climbing activity Fig. 4B ($f(1, 13) = 4.80$, $P<0.05$, n=8/group) as compared to control mice.

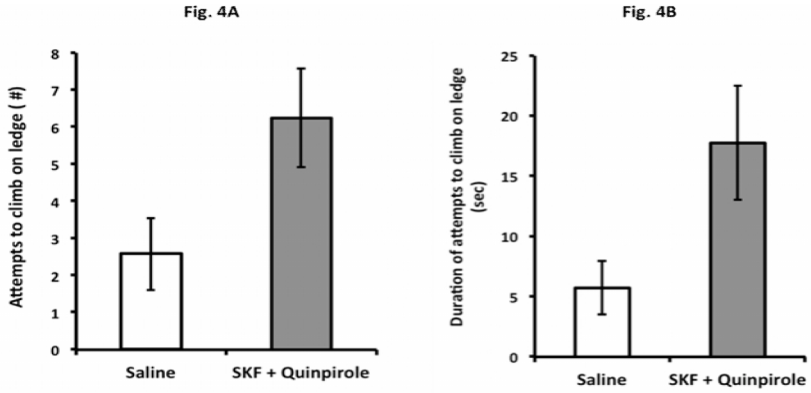

Fig. 4. Effects of SKF + Quinpirole on potentiation of IL-2 induced activity. (4A) shows significant effect of SKF + Quinpirole on attempts to climb on the ledge. (4B) shows significant effects of SKF + Quinpirole on duration of climbing on the ledge

Combined administration of SKF and Quinpirole, without prior IL-2 injection, did not show any difference in attempts to climb on ledge Fig. 5A ($f(1, 4) = 0.052$, $P = 0.82$, n=3/group) as well as duration of attempts to climb on ledge Fig. 5B ($f(1, 4) = 0.033$, $P = 0.86$, n=3/group).

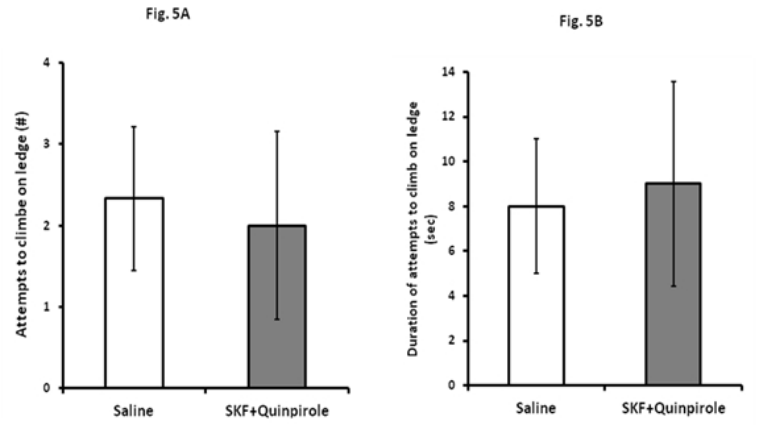

Fig. 5. Effects of SKF + Quinpirole on naïve mice. (5A) shows no significant effects of SKF+ Quinpirole on attempts to climb on the ledge. (5B) shows no significant effect of SKF + Quinpirole on duration of climbing on the ledge

4. DISCUSSION

The main finding of the present investigation is that repeated injections of IL-2 induce an acquired behavioral response pattern that requires concurrent stimulation of dopamine D1 and D2 receptors. An implication of this finding is that sub-chronic or chronic elevations of IL-2 may produce an acquired behavioral response that persists beyond the presence of IL-2. Accordingly, these findings identify a process by which IL-2 treatment (and perhaps sub-acute or chronically elevated levels of IL-2) produces long-lasting behavioral abnormalities that persist after IL-2 levels have returned to- or even below baseline. In this regard, the present findings may help reconcile seemingly disparate findings that either decreased or increased levels of IL-2 are associated with psychopathological outcomes (e.g., schizophrenic-like behavior).

Most studies evaluating the effects of IL-2 on behavior use single injections paradigms [3,8,9]. Some studies using repeated injections paradigms have focused on anxiety-related behavior [13,16]. We previously showed that repeated home-cage injections of IL-2 induce an increase in climbing behavior [12] in the present study we elaborate on this finding by showing that when tested in a novel environment, repeated injections of IL-2 induce progressive increases in rearing/sniffing and climbing behavior.

There is strong evidence that dopaminergic acting drugs require co-stimulation of D1 and D2 receptors for maximal induction of stereotypic behavior [17-19]. Stereotypic behavior is viewed as an acquired behavioral response that is subserved by co-activation of these receptors. Canales and colleagues showed that co-administration of SKF 81297, a D1 receptor agonist, and quinpirole, a D2 receptor agonist, 1- day after cessation of a repeated cocaine injection regimen produced stereotypy in these animals. Administration of the individual receptor agonists had no effect [17]. Hence, after repeated psychostimulant injections, concurrent activation of D1 and D2 receptors are required to produce the same behavioral response pattern. We suggest that a similar process is associated with chronic elevations of IL-2, which increase the likelihood that repetitive stereotyped movements will be expressed or induced by other stimuli or events that stimulate dopamine D1 and D2

receptors. An implication of these findings is that chronic IL-2 elevations could predispose the individual to drug seeking or taking behavior.

Regarding IL-2 and dopaminergic processes and related behaviors, we have shown that repeated IL-2 injections produce long-lasting increases in sensitivity to the motor-stimulating effects of GBR 12909, a highly selective dopamine uptake inhibitor (GBR 12909) [10] Single microinjections of IL-2 into nigrostriatal sites induce more severe disturbances in motor activity, which include rotational behavior and asymmetric body posture [20].

Little is known about underlying mechanisms and behavioral processes. Here, we determined whether repeated injections of IL-2 paired with a novel environment induce a behavioral response not evident following a single injection. Of further importance, we sought to identify the mechanisms underlying the development and expression of this response. Inasmuch as IL-2 is implicated in psychiatric disorders associated with an increase in repetitive behaviors and that are treated with drugs that target, at least in part, dopamine D1 and D2 receptors, we sought to determine whether IL-2 induces an acquired behavioral response pattern requiring concurrent stimulation of D1 and D2 receptors. Stereotypic motor behaviors comprise a group of species-specific adaptive motor behaviors and cognitive responses that help the individual cope with environmental conditions [21,22]. In rodents, the exploration of novelty involves a variety of stereotyped motor behaviors, including sniffing, digging, gnawing, biting, rearing, and climbing behavior. The individual will additionally use stereotyped patterns of attention, planning and cognition. However, the abnormal repetition of these motor and cognitive stereotypies (e.g., repetitive sniffing, inflexible patterns of attention) without an adaptive purpose is a fundamental component of various CNS disorders. Although the mechanisms underlying repetitive motor stereotypies are not entirely understood, the mesostriatal system is presumed to play a central role. Indeed, there is a general consensus that this behavioral response pattern is associated with coordinate changes in neuronal activation in the striatum and stimulation of dopaminergic receptors [23-25]. Direct evidence that IL-2 can induce psychiatric abnormalities that are associated with aberrations in the mesostriatal system stems from clinical trials utilizing IL-2 to treat cancer and AIDS patients. Patients receiving chronic high dose cytokine therapy display psychosis and cognitive deficits [26-28]. Chronic subcutaneous IL-2 therapy also results in psychopathological outcomes [29]. For example, significantly increased scores on the Minnesota Multiphasic Personality Inventory (MMPI) were evident in scales of schizophrenia and psychopathic deviate, conversion hysteria, depression, and psychasthenia. The psychopathological outcomes associated with IL-2 therapy appear to be directly related to cytokine administration, since they are not typically evident prior to onset of therapy, although the likelihood that a psychopathological outcome is induced following onset of therapy may be enhanced in patients with a history of such an outcome.

Moreover, the present experiment would also provide the first direct in vivo evidence that interplay between a cytokine (IL-2) and a monoaminergic receptor in the expression of an acquired behavioral response. It should also be noted that in parallel, coordinate increases in neuronal activation patterns are induced in the rostral striatum [17].

Collectively, these data show that IL-2 is associated with stereotypic movements. These effects are dose dependent and enhanced with repeated doses. IL-2 induced climbing effects are not due to escape activity as IL-2 treated mice showed escape deficits. IL-2 governed effects are due to involvement of dopamine receptors. Either Dopamine D1 or Dopamine D2 receptor is involved in development of IL-2 induced behavioral changes, however both D1 and D2 are required for expression of IL-2 induced stereotypies.

Behavioral changes seen after repeated IL-2 injections can be enhanced by administration of dopamine agonists.

5. CONCLUSION

The main finding of the present investigation is that repeated injections of IL-2 induce an acquired behavioral response pattern that requires concurrent stimulation of dopamine D1 and D2 receptors. An implication of this finding is that sub-chronic or chronic elevations of IL-2 may produce an acquired behavioral response that persists beyond the presence of IL-2. Accordingly, these findings identify a process by which IL-2 treatment (and perhaps sub-acute or chronically elevated levels of IL-2) produces long-lasting behavioral abnormalities that persist after IL-2 levels have returned to- or even below baseline.

CONSENT

Not Applicable.

ETHICAL APPROVAL

All authors hereby declare that "Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985) were followed, as well as specific national laws where applicable. All experiments have been examined and approved by the appropriate ethics committee

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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