Article *NIMHANS Journal*

Apomorphine-Induced Time-Dependant Potentiation of Dopamine Post-Synaptic Receptor Response

Volume: 08 Issue: 01 January 1990 Page: 53-55

~~Chittaranjan Andrade .~~

Reprints request
, S Arunasmitha, N Pradhan,
- *Department of Psychopharmacology, National Institute of Mental Health & Neuro Sciences, Bangalore 560 029, India*

Abstract

Dopaminergic agonists have sporadically been reported to produce paradoxical sensitization of dopamine (DA) receptors; the phenomenon has however been poorly studied. We demonstrate in this report that the administration of a single (high) dose of apomorphine augments DA post-synaptic receptor-mediated locomotor response in the Sprague-Dawley rat at a time span of as long as week after the original injection. The theoretical and experimental implications of these findings are discussed.

Key words -
Apomorphine,
Dopamine post-synaptic receptors,
Paradoxical sensitization of receptors,
Locomotor response,
Sprague-Dawley rats

It is well-known that the chronic administration of drugs (eg., chlorpromazine, haloperidol) which interfere with dopaminergic neurotransmission produces augmented agonist-elicited dopamine (DA) post-synaptic receptor responses, while the chronic administration of DA agonists in general has the opposite effect. Increase and decrease respectively in both receptor number and receptor sensitivity in are responsible for these effects [1]. It has been recognized for about a decade that DA agonist administration can also produce a paradoxical sensitization of the post-synaptic receptors, the necessary prerequisite for this paradoxical response being the spaced rather than the massed administration of the agonist [2]. Although unusual, this paradoxical effect has been poorly studied. In view of the potential theoretical and experimental implications, in the present study we sought to assess whether the administration of a single dose of a DA agonist (apomorphine) can produce prolonged sensitization of the DA post-synaptic receptors in the rat brain.

Material and Methods

The apomorphine-induced motility-alteration behavioural paradigm was used to describe potential changes in DA post-synaptic receptor responses. In low doses, apomorphine (a direct DA agonist)

stimulates the (inhibitory, pre-synaptic) DA autoreceptors, leading to a reduction in animal motility. In high doses apomorphine stimulates the (excitatory) DA post-synaptic receptors, leading to an increase in animal motility [3], [4]. The use of high dose apomorphine in this study permitted a direct assessment of DA post-synaptic receptor functioning.

Twenty-four adult, male Sprague-Dawley rats (160-200 gm), housed two per cage with free access to tap water and standard laboratory diet, were brought into a temperature and humidity controlled, 12 hour light-dark cycle (lights on at 6 a.m.), sound proof, insulated room one week prior to starting the experiment, and were maintained in this environment until the end of the study.

In each pair, one rat was subcutaneously (nape of the neck) injected with normal saline (1 ml/kg) and the other with freshly dissolved (2 mg/kg) apomorphine (SIGMA Chemicals) in a volume of 1 ml/kg.

Between 9 and 11 a.m. on the 7th day after the above injection, the rats were monitored on a motility parameter of DA post-synaptic receptor functioning: 20 minutes after a subcutaneous (nape of the neck) injection of freshly dissolved (2 mg/kg in a volume in 1 ml/kg) apomorphine, the rats, one at a time, were placed in a glass cylinder measuring 22 cm in internal diameter and 45 cm in height, and the number of quadrants (marked on the floor of the cylinder) crossed by the rat during a 3 minute monitoring period was noted by an experienced observer blind to the experimental status of the rats. The procedure followed that which has been described for the small open field [5].

Results

Rats pretreated with apomorphine (experimental group) exhibited a (mean ± S.D.) motility (in terms of quadrants crossed during the period of monitoring) of 69.9 ± 33.9 while rats pretreated with saline (control group) exhibited a motility of 42.4 ± 19.5. The raw motility scores were subjected to log transformation to homogenize the variances between the two groups; using the independant sample Student's t test, the experimental group was found to be significantly more motile than the control group ($t=2.29$, $p<0.05$).

Discussion

The greater motility in the experimental group indicates that pretreatment with high dose apomorphine enhances DA post-synaptic receptor-mediated behavioural responses to a repeat challenge with the receptor agonist; the methodology used in his study however precludes speculation on whether upregulatory, supersensitization or both mechanisms are involved in the production of such a response, and radioligand binding techniques in future experiments may be utilised to address this issue.

The poorly studied phenomenon of DA agonist-induced time-dependant paradoxical behavioural sensitization has been recently reviewed [2]. With the exception of Castro et al [2] who demonstrated that the single administration of high dose apomorphine and repeated (well spaced) administration of low dose apomorphine both sensitize DA post synaptic receptors as a delayed effect, no systematic data are available describing either magnitude of agonist challenge required to produce the effect or duration of paradoxical response if it obtains. Thus, to our knowledge, ours is the first study to report that a single challenge with high dose apomorphine (2 mg/kg) behaviourally sensitizes the DA

post-synaptic receptors at an interval of as long as a week after the challenge.

This finding has important theoretical implications. Receptor effects have been suggested to represent the mechanism of action of various biological therapies in psychiatry. For example, in mooting a hypodopaminergic aetiology of depression. Willner [6] has suggested that the efficacy of electroconvulsive therapy and antidepressant drugs lies in their ability to (amongst other effects) augment to dopamine post-synaptic receptor responses. The study of Castro et al [2] demonstrated that these very receptor changes may be obtained 2 days after challenge with a single injection of high dose apomorphine; the present study demonstrates that such receptor changes persist for at least a week. The facility with which these receptor effects are obtained suggests that Willner's [6] hypothesis may be simplistic- else, spaced challenge with high dose apomorphine should have antidepressant action!

Viewed from a different angle, it is worth exploring the possibility that spaced as opposed to massed agonist/antagonist challenges to various neurotransmitter systems exert receptor effects that have therapeutic potential. One such application of this precept has been suggested for the management of tardive dyskinesia [7], [8].

The finding of this study also has experimental implications. Firstly, experiments requiring a behavioural model of supersensitive DA post-synaptic receptors [7], [8] may utilize the model extant in this study as opposed to, for example, the less economical (in terms of time and energy) model involving chronic neuroleptic treatment. Secondly, where independent results are desired, obtaining repeat measures of testing in animals previously challenged with apomorphine may not be an acceptable procedure; Waddington's [9] tentative note of caution in this regard is, in the light of the finding of this study, clearly too mild.

This preliminary report from our laboratory is a prelude to the systematic investigation of the doses and schedules of agonist administration required to produce paradoxical receptor changes, and to the description of the time course of DA auto-receptor and post-synaptic receptor changes when they do occur in their circumstances.

Acknowledgement

We thank Prof. Jan M Van Ree, Rudolf Magnus Institute for Pharmacology. The Netherlands, for his clarification in this research.

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