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TARDIVE DYSKINESIA: A POTENTIAL NEW NEUROCHEMICAL ANIMAL MODEL

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SUMMARY

Conventional neurochemical animal models of tardive dyskinesia are based upon the production of dopamine postsynaptic receptor supersensitivity by the chronic administration of neuroleptics. This study demonstrates that the same result is obtained by injecting Sprague-Dawley rats with a single ('high') dose of apomorphine. It is hence suggested that apomorphine-induced time-dependant potentiation of dopamine-postsynaptic receptor response may be a more convenient neurochemical animal model of tardive dyskinesia; related theoretical and practical issues are discussed briefly, as also the methodological differences between the present study and an earlier report.

Animal models of human illness states are necessary to conveniently investigate pathophysiological processes. Available models for tardive dyskinesia (TD) are based upon the production of dopamine (DA) postsynaptic receptor supersensitivity (the putative neurochemical basis of TD) by the chronic administration of neuroleptic drugs. This model is essentially neurochemical as in rodents, unlike as in primates, no movement disorder is apparent (Goetz et al., 1983). It may hence be argued that whatever the means by which such a change is elicited, the production of supersensitive DA postsynaptic receptors could constitute a neurochemical animal model of TD. The present study expands upon an earlier report (Andrade et al., 1990) that a single 'high' dose apomorphine challenge produces time-dependant potentiation of DA postsynaptic receptor response, suggesting that restricted apomorphine challenge could replace the need for chronic neuroleptic administration in rodent models of TD.

Methodology

Eighteen adult, male, Sprague-Dawley rats (160-200 gm in body weight) obtained from the Central Animal Research Facility at the National Institute of Mental Health and Neurosciences (Bangalore) were housed two per cage with free access to tap water and standard laboratory diet. The animals 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 before commencement of the experiment, and were maintained in this environment until the end of the study.

Dopamine postsynaptic receptor function was studied using the apomorphine-induced behaviour alteration paradigm: in high doses (e. g. exceeding 1 mg/kg body weight) apomprphine, a direct DA agonist, stimulates the DA postsynaptic receptors leading to stereotypic behaviour and hypermotility; quantification of this behaviour change yields an index of receptor function (Nilsson and Carlsson, 1982; Arunasmitha et al., 1989). In the present study, apomorphine was used in the dose of 2mg/kg body weight, and the behaviour selected for quantification was animal motility.

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In each cage, one animal (experimental) was subcutaneously (nape of the neck) injected with freshly-dissolved apomorphine (SIGMA chemicals, USA) in a vehicle (normal saline) of volume 1 mg/kg body weight, while the other animal (control) was injected with vehicle alone.

Twenty minutes after the injection, the motility of each animal was assessed according to the procedure described for the small open field (Van Ree and de Wied, 1988): the animal was placed in a glass cylinder measuring 45 cm in height and 22 cm in internal diameter, and the number of quadrants (marked on the floor of the cylinder) crossed by the animal during a 3 minute monitoring period was noted by a trained observer blind to the experimental status of the rats. Motility monitoring was conducted between 9 a.m. and 11 a.m. to control for diurnal variation in motility.

One week later, the injections and monitoring were repeated in an identical fashion. The change in motility scores across time in the experimental group describes the change in DA postsynaptic receptor function as elicited by the initial apomorphine challenge in this group, while the behaviour of the saline-injected group serves to control for handling and environment related effects.

Results

The baseline and one week post-baseline motility scores in the experimental and control groups are presented in the Table. A two group two way repeat measures ANOVA revealed a significant main effect for groups ($F=27.53$, d. f. = 1, 16, $p<0.001$) which indicates that the experimental group was significantly more motile than the control group (which result is expectable, as apomorphine enhances motility via DA postsynaptic receptor mechanisms), a non-significant main effect for the time ($F=4.32$, d. f. = 1,16, N. S.) which indicates that, considered together, the two groups did not change significantly across time, and a significant group × time interaction effect ($F=7.32$, d. f. = 1,16, $p<0.025$) which indicates that there was significant increase in motility in the experimental group across time, as distinct from the change in scores in the control group.

TABLE—*Mean±SEM quadrants crossed by experi mental and control rats at baseline and one week post-baseline*

	Baseline	One week post-baseline
Experimental (n=9)	51.44 ±9.86	71.78 ±11.19
Control (n=9)	11.67 ± 0.75	9.0 ± 2.01

Discussion

As apomorphine-elicited motility significantly increased (across time) in the experimental group relative to the control group, one must conclude that the DA postsynaptic receptors (responsible for the motility in the experimental group) had become supersensitive to apomorphine i.e., fulfilling the requirements for the neurochemical basis of TD.

It is well-known that, in general, the chronic administration of DA agonists (e.g. L-dopa) diminishes while the chronic administration of DA antagonists (e.g. haloperidol) increases agonist-elicited (e.g. using apomorphine) DA postsynaptic receptor responses; however, it has recently been recognized that the spaced (as opposed to the masses or chronic) administration of a DA agonist can paradoxically sensitize these postsynaptic receptors (Rebec, 1984; Castro et al., 1985). The present study demonstrates that even a single 'high' dose of apomorphine can sensitize DA postsynaptic re-

ceptors at a period extending upto at least 1 week after the challenge.

An earlier study (Andrade et al., 1990) had described apomorphine-induced time-dependant potentiation of DA postsynaptic receptor response using an experimental design wherein receptor function was studied *cross-sectionally* in animals pre-treated with apomorphine or saline; the present study describes the same results using an experimental designs wherein receptor function was studied *longitudinally* in animals treated with apomorphine or saline. In other words, the former study described DA postsynaptic receptor supersensitivity relative to a control group at a single point in time, while the present study describes DA postsynaptic receptor supersensitivity actually developing across time. The two studies may thus be considered to complement each other.

There is no reason to suppose that DA postsynaptic receptor supersensitivity produced by one means is any different from that produced by another means; hence, however elicited, these receptor changes, when occuring, could equally be considered as models of TD. Chronic neuroleptic administration requires 3 weeks for the production of the necessary receptor changes in rats (Goetz et al., 1983); this is far more troublesome and time-consuming than the present method wherein a single injection of apomorphine suffices to elicit the desired effects. Further research is warranted to describe the relative extent (in various DA systems in the brain), magnitude and duration of receptor change as produced by the two methods.

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