Apomorphine as a preferential stimulant of self-inhibitory dopamine receptors in man

G. U. CORSINI (a), M. DEL ZOMPO (a), M. P. PICCARDI (a), A. MANGONI (a) and G. L. FESSA (b)

(a) Institute of Neurology, University of Cagliari
(b) Institute of Pharmacology, University of Cagliari

The emetic action of apomorphine in man prevents the administration of doses exceeding 40-100 µg/kg. This is presumably why no effects ascribable to postsynaptic dopamine (DA) receptor stimulation may be observed, except for parkinsonian patients, in which apomorphine proved to have a certain therapeutical activity [1-3]. Most likely, in these subjects postsynaptic DA receptors in the basal ganglia are supersensitive.

In man, non emetic doses of apomorphine may elicit objective changes, such as sedation, sleepiness, yawning, hypotension and eyelid ptosis, as well as subjective effects such as sadness, malaise and light-headed feeling [4, 5], which are difficult to ascribe to the stimulation of postsynaptic DA receptors. On the contrary, since similar effects are elicited by neuroleptic drugs, the functional changes induced by non emetic doses of apomorphine in man might be interpreted as being the result of a decreased dopaminergic activity. Such interpretation arises also from the consideration of the results obtained with apomorphine in neurological and psychiatric conditions.

Sedation and sleep induced by non emetic doses of apomorphine in humans

The intramuscular administration of 20 µg/kg of apomorphine to 12 male volunteers induced sedation in 8 subjects, 5 of which also showed sleep. The sedative and sleep-inducing effects of apomorphine were prevented by haloperidol (1 mg), pimozide (1 mg) and by sulpiride (10 mg), but not by promethazine (25 mg) or amitriptyline (25 mg) [6].

Similar results were obtained in schizophrenic patients [6]. In these patients, in contradistinction to the results obtained in the acute treatment,
the chronic administration of haloperidol prevented the sedative effect of 10 mg of apomorphine. The sedative effect was also prevented by pimozide and particularly by sulpiride, suggesting that it was due to the stimulation of DA receptors.

The problem is whether DA receptors responsible for sedation and sleep in humans are the self-inhibitory DA receptors or a special kind of post-synaptic DA receptors sensitive to low concentrations of the transmitter. While the above results indicate that non emetic doses of apomorphine favour sleep, the use of a single intramuscular administration of the drug does not allow to distinguish direct effects of the drug from rebound compensatory changes in sleep parameters. For this reason, we have recently studied the effect of intravenous infusion of apomorphine on human sleep [7].

Apomorphine was given to ten subjects (4 male and 6 females) at a non emetic dose, ranging from 10 to 15 μg/min according to the patient. The infusion began at 10 p.m., at the time the subjects would normally fall asleep, and lasted for 240 min. Apomorphine infusion totally suppressed REM sleep and decreased by more than 90 percent the amount of delta sleep. Thus, the EEG pattern during apomorphine infusion is characterized almost exclusively by the presence of stages 1 and 2 sleep.

The effect of apomorphine on sleep was prevented by haloperidol and sulpiride in doses which per se did not modify sleep parameters. Although there is reason to assume that apomorphine-induced changes on sleep parameters are due to stimulation of DA receptors, it is unlikely that these receptors may be ascribed to the DA self-inhibitory ones. In fact, the effect of apomorphine are opposite to those observed in humans with specific inhibitors of catecholamine synthesis [8] and with DA receptor blockers [9].

On the other hand, the suppressant effect of apomorphine on REM sleep resembles that obtained with amphetamine and with the intravenous infusion of L-DOPA [10]. In humans, as opposed to observations on rodents, apomorphine does not produce insomnia. It is possible that the doses of apomorphine that can be used in humans are insufficient to affect DA receptors involved in arousal. However, species differences in sleep mechanisms are well known [11]. The physiological implication of the above results might be that the stimulation of some kind of DA receptors might be involved in the onset of light sleep which in turn facilitates the progression into the other sleep stages. However, an abnormal persistence of DA stimulation, such as that produced by apomorphine infusion, might maintain NREM light sleep and prevent the development of a normal sleep. Interestingly, marked decreases in the amount of REM sleep and delta sleep have been noted in acute schizophrenies [12], a condition in which DA hyperstimulation has been suggested.

Improvement of choreic movements

Apomorphine has been reported to ameliorate the involuntary movements (A.I.M.) in five patients affected by Huntington's Chorea (H. C.) [13]. This finding is in apparent contrast with the accepted view that an increased dopaminergic activity, due to striatal DA receptor hypersensitivity, is responsible for the neurological disorders present in this disease [14]. Indeed, according to this theory, apomorphine would have been expected to worsen the A.I.M., as it actually does in experimental models of H. C. in monkeys [15]. Recently, however, amelioration of A.I.M. has been confirmed and evidence that apomorphine-induced improvement in H. C. is due to stimulation of DA receptors has been presented [16]. In fact, the intramuscular injection of non vometic doses of apomorphine (from 1 to 4 mg) to four patients, with a well-defined history of H. C., induced a marked but short-lasting decrease of A.I.M. evaluated by means of a polygraphic recording. Pretreatment with haloperidol (2 mg i. m.) or sulpiride (100 mg i. m.) 30 minutes before apomorphine, prevented the effect of this compound. These data suggest that the antichoreic effect of apomorphine may well be explained by a preferential stimulation of self-inhibitory DA receptors resulting in inhibition of dopaminergic transmission.

These observations further support evidence of a regulatory role of DA on A.I.M. in this disease, although dopaminergic transmission may not be necessarily impaired.

The proposed mechanism, by which apomorphine improves the A. I. M. in H. C. may better explain other paradoxical effects of this drug on different neurological syndromes such as the therapeutic activity on tardive dyskinesia [17, 18], acute dystonic reaction by neuroleptics [19], spasmodic torticollis [20], Gilles de la Tourette syndrome [21]. Therefore, if all these effects are due to decreased dopaminergic transmission via self-inhibitory DA receptor stimulation, we have to assume that the stimulation of postsynaptic DA receptors responsible for the anti-parkinsonian effect of apomorphine represents an exception rather than a rule in the mechanism of action of this drug.

Improvement of manic and schizophrenic symptoms

Many of the functional changes induced by low doses of apomorphine in man, as presently described, are shared by neuroleptic drugs which are well known for anti-psychotic activity. Therefore, considering the proposed mechanism of action of apomorphine in man, we were led to investigate a possible therapeutic efficacy of this drug in psychotic syndromes.
Previous reports on this matter have claimed that unexpectedly apomorphine did not worsen schizophrenic symptoms[22]. On the contrary a DA agonist, piribedil, at low doses proved to have some anti-manic properties in a double-blind long term study on three patients[23]. Similar antimanic responses to piribedil in two out of seven patients have been described by other AA., but a dose–response relationship has not been reported[24].

Our experience on manic patients is consistent with a well defined antimanic activity of apomorphine[25]. Seven unmedicated patients affected by an acute episode of mania in the course of manic–depressive psychosis were treated with a non-emetic dose of apomorphine (1 mg i. m.). A few minutes later, three out of the seven patients showed marked signs of psychic and motor sedation with a marked reduction of euphoria. This effect lasted from 20 to 50 min, after which the responsive patients returned to their previous behaviour with the exception of one subject who subsequently worsened very much. This study strongly supports evidence for the antimanic properties of DA agonists; however, due to the side effects and the short duration of apomorphine action this kind of clinical trial may have a questionable value. Thus pallor, nausea, hypotension, sedation and sleepiness which often occur after apomorphine, even at low doses, made such a study difficult or even impossible to perform in a double blind design.

Similar limitations apply to our trial directed to evaluate the antischizophrenic properties of apomorphine. Thus, to mitigate this problem, Smith and Coll., who have recently described an improving effect of apomorphine on schizophrenic symptoms, used double blind placebo controlled procedures with video tape[26]. This procedure allowed to the «blind» experimenter to evaluate psychic conditions only during the period of time free from side effects, carrying out in this way a more reliable double blind study. In our experience, however, apomorphine (1 mg i.m.) caused rapid but temporary reduction of the symptomatology in 6 out of 18 schizoaffective patients, in 8 out of 24 paranoid and in 7 out of 12 hebephrenic schizophrenics. In responsive subjects the amelioration included most features of the psychotic symptomatology (delusions, cognitive disturbance, bizarre or inappropriate behaviour, suspiciousness and aggressiveness). In contrast, apomorphine was ineffective in all 4 of the catatonic schizophrenics studied. The improvement was evident only in patients who were not under neuroleptic therapy. In fact the responsive subjects after ten days of haloperidol treatment do not show any psychic change after apomorphine further administration, indicating that this effect is antagonized by neuroleptics. In accordance with other studies[22], apomorphine administration did not worsen appreciably the psychotic symptomatology of our patients as it has been showed to occur after amphetamine[27], or methylphenidate[28].
and this fact further indicates that apomorphine, at low doses, does not activate postsynaptic DA receptors, but, on the contrary, may effectively and acutely impair dopamine activity. It is possible, therefore, that such an effect is due to a stimulation of self-inhibitory DA receptors.

Thanks to this new experimental approach, more selective drugs acting on different brain DA receptors might represent a new therapeutical strategy in the management of some neuropsychiatric disorders. Despite the indirect nature of clinical evidence, it nonetheless remains that the suggested existence of different types of DA receptors constitutes the basis for a better understanding of physiological mechanisms regulating some brain functions.

Summary. — In man, non emetic doses of apomorphine elicit a series of behavioural, neurological and psychological changes which are difficult to ascribe to the stimulation of postsynaptic dopamine receptors. Since similar effects are elicited by neuroleptic drugs, the functional changes induced by apomorphine in man might be interpreted as being the result of a decreased dopaminergic activity. The sedation and sleep, the improvement of choreic movements and the antipsychotic effect induced by non emetic doses of apomorphine are prevented by specific dopamine receptor blockers. These responses therefore are mediated through a stimulation of dopamine receptors leading to a decreased dopaminergic transmission.

This new type of receptors might be identified with the so called «self-inhibitory» dopamine receptors.

REFERENCES


