TARDIVE DYSKINESIA: CONCEPTS AND PROSPECTS

Department of Psychoneuropharmacology, Faculty of Medical Sciences, Catholic University of Nijmegen, The Netherlands
A. R. Cools

Tardive dyskinesia is a somewhat ill-defined syndrome which has challenged scientists and clinicians for many decades. Until now, the exact mechanisms underlying this syndrome are unknown and there is no successful treatment available. The purpose of this contribution is neither to furnish clinical guidance, nor to provide a complete survey of all the research that has been done in the field of tardive dyskinesia. Instead the goal is to focus on a number of therapeutically promising research developments, which come direct from the laboratory and have yet to be translated into clinical practice. The weight given to anatomical–pharmacological–behavioural research in this contribution reflect the weight given to such research in the field today.

Tardive dyskinesia is defined as an iatrogenic extrapyramidal disorder produced by longterm administration of antipsychotic drugs; it is characterized by oro-lingual-buccal dyskinesias that usually resemble continuous chewing motions with intermittent darting movements of the tongue and abnormal movements of the lips whereas there may also be choreathetoid movements of extremities. However, comparable syndromes of abnormal involuntary movements have already been described long before the introduction of antipsychotic drugs in a broad spectrum of medicated and unmedicated people, among others, in schizophrenia, encephalitis epidemica, chorea of Huntington and Parkinson’s disease. Despite the fact that the movements, as described in the differential neurological/psychiatric disorders, are quite similar, it is not known whether these movements are behavioural indications of a comparable pathogenesis in these different disorders. No adequate universally applicable diagnostic instrument or parameter is available for defining type and intensity of the dyskinesias. Tardive dyskinesia is in general assessed by means of rating scales; the latter is not a very reliable method. There are no consistent data about the prevalence of tardive dyskinesia. This is partly due to the possibility that the development of tardive dyskinesia is the result of an interplay between drugs such as antipsychotics and neurological and/or psychiatric disturbances. Apart from age, gender, cognitive dysfunction, negative symptoms of schizophrenia and structural brain pathologies which all are believed to contribute to the development of tardive dyskinesia, cumulative exposure to neuroleptic drugs is known to be one of the main risk factors for the development of tardive dyskinesia. Many attempts have been made to understand the pathogenesis of tardive dyskinesia. The biochemical substrate of tardive dyskinesia is still unknown despite decades of clinical and animal research. Nevertheless, several hypotheses have been postulated on various grounds. The hypothesis that both an up-regulation and a supersensitivity of dopamine receptors in striatal structures give rise to tardive dyskinesia has long been the leading hypothesis. The main shortcoming of this theory is that it does not adequately explain the coexistence, in some cases, of tardive dyskinesia and Parkinsonism. The imperfections of this so-called “disuse supersensitivity” hypothesis leave room for other productive theories. The hypothesis that a dysbalance between distinct, striatal dopamine receptors underlies tardive dyskinesia is a promising theory that
may pave the way to better therapy of tardive dyskinesia. Apart from this hypothesis that will be elaborated in more detail, nearly all neurotransmitters have found a place in one or another theory about the pathophysiology of tardive dyskinesia. The noradrenaline theory is based on the function of noradrenaline as modulator of dopaminergic systems and therapeutic experiences. The hypoactivity of acetylcholine in tardive dyskinesia is the basis for a cholinergic theory of the disorder. Since tryptophan has been found to improve the condition in some patients suffering from tardive dyskinesia, a serotonin deficiency has been implicated. Research into the GABA system in tardive dyskinesia is based on the finding that a chronic neuroleptic treatment not only causes loss of GABAergic striatopallidal neurons, but also decreases GABA-activity in pallidal structures. The peptide theory of tardive dyskinesia emphasizes the role of cholecystokinin octapeptide as a neuromodulator of dopamine systems in striatal structures. The free radical hypothesis is based on the finding that free radicals which are known to be formed as metabolic products of neuroleptics, cause structural damage that may contribute to the pathogenesis of tardive dyskinesia.

The main shortcoming of all these theories is that they have not led to new therapies. Furthermore, the different hypotheses are quite diverse which may be due to the fact that tardive dyskinesia is not a unitary syndrome, and multiple causes may be superimposed. Apparently, we know too little about the specific neuronal substrate that is involved in tardive dyskinesia in order to understand the syndrome itself, as well as the different associations with other neurological and/or psychiatric disorders. It is believed that knowledge of the neuronal substrate forms the basis for new developments in animal models which in turn inspire new treatments. This fruitful connection between the animal and clinical models should pave the way to better therapy of tardive dyskinesia. For that reason, the main part of the contribution will be devoted to the latest developments in this rapidly changing field.