Editorial

COMT as a Drug Target for Nervous System Disorders

Catechol-O-methyltransferase (COMT) [1] is a key enzyme involved in the methylation of catechol structures, including dopamine, norepinephrine, epinephrine, caffeine, and catechol estrogens. In the last decade, there has been renewed interest in this enzyme because of the findings that implicate it in the development and manifestations of mental illnesses. It is now commonly accepted that COMT's most crucial effects are centered in the modulation of prefrontal cortex (PFC)-mediated functions. This might be explained by the major determinant role of COMT in PFC dopaminergic signaling, which is critical for modulating higher order cognitive functions, thereby impacting many domains of human behavior, thought and emotion. However, also regions of the nervous system other than the PFC and biological effectors apart from dopamine might be affected by COMT. This possibility is still less explored and will need to be addressed in future studies. Nevertheless, COMT pleiotropic behavioral effects seem consistent and real. In particular, from studies conducted in both mouse models and humans, COMT enzyme activity seems to be involved in an apparent evolutionary trade-off between cognitive and affective functions [2-4]. The knowledge acquired so far, indicate COMT as an attractive drug target potentially having important implications for several disorders of the nervous system. Indeed, as it is evident from the review manuscripts in this special issue, the activity of COMT has been linked to a large spectrum of human phenotypes, including cognition, pain sensitivity, personality, anxiety, psychosis and reward processing. Notably, the level of COMT enzyme activity presents individual changes in the human population because of common functional genetic mutations. Genetic variations in COMT may have important implications in the clinical setting, as changing COMT activity could impact the efficacy and dosing of a particular therapeutic treatment and/or intervention. Therefore, functional genetic variations in COMT are factors that will probably need to be considered in the rational design of more effective and personalized healthcare.

In line with this view, this issue presents some of the current knowledge on COMT in an attempt to provide indications on how to consider this enzyme and its genetic variations for the treatment of abnormalities in behavioral domains such as cognition, pain sensitivity, personality, sleep, and reward processing. Similarly, this can be applied in the management of some neuropsychiatric phenotypes in pathologies such as personality-related disorders, chromosome 22q11 microdeletion syndrome, schizophrenia, depression, Parkinson's and Alzheimer's diseases. While not all-inclusive by any means, these chapters will illustrate the broad potential of COMT in the advancement of specific clinical treatments and/or interventions.

COMT AND COGNITION

In the opening article, Sambataro and colleagues provide a literature overview supporting a role of COMT genetic variation in cognitive as well as structural and functional brain changes associated with senescence. The modulatory function of genetic and non-genetic factors on the neural and cognitive effects of COMT in late life is also discussed. This work might then provide inputs on the use of COMT for treatments aiming to improve cognitive efficiency in aging. COMT-dependent mechanisms in modulating cognitive functions are not static relative to age. Indeed, in the second chapter of this issue, Scheggia *et al*. analyze the implications of COMT in cognitive functions and dysfunctions following developmental trajectories from adulthood to childhood. In particular, the authors discuss how COMT genetic variants may predict individual variations in selective cognitive abilities including executive control, working memory, attentional control and long-term memory. Furthermore, they discuss how COMT genetic variants may be implicated in cognitive abnormalities present in some neuropsychiatric disorders even from early developmental stages, and how the COMT genotype may represent the basis for individual variations to treatments.

COMT AND AFFECTIVE/PAIN FUNCTIONS

Segall and coworkers delineate the relevance of COMT in complex human pain conditions. This review will truly help provide a level playing field for researchers in mechanisms of pain function. In particular, the role of peripheral and spinal adrenergic signaling in modulating nociceptive and neuropathic pain is analyzed. A hypothesis is presented that illustrates how there might be a fundamental difference between the contribution of COMT activity to neuropathic and nociceptive pain modalities. This is followed by another excellent manuscript that provides a thorough review of the association between COMT (rs4680, Val/Met) genotype and anxiety related phenotypes by Montag and colleagues. A solid and scholarly introduction to biological theories of personality is also provided.

COMT IN PSYCHIATRIC DISORDERS

The next manuscripts in this issue deal with the implication of COMT in specific abnormal phenotypes in neuropsychiatric disorders. This topic is first addressed by Espinoza *et al*., who focus on the role played by COMT and related processes in the pathophysiology and pharmacology of Parkinson's disease. In particular, the critical mechanisms affected by COMT that may influence the therapeutic or side effects of L-DOPA treatment, the recent progress in the development and clinical use of COMT inhibitors and the genetic studies highlighting the role of this enzyme in Parkinson's disease pathogenesis and treatment, are discussed.

Kocabas instead provides an overview of various pharmacogenetic studies about the role of COMT in the modulation of antidepressant treatments in major depressive disorder.

Afterward, three review manuscripts investigate different aspects of the involvement of COMT in distinct features of schizophrenia-related disorders. Armando and colleagues present a selected literature on the 22q11.2 deletion syndrome. This is a genetic syndrome characterized by high rates of psychiatric morbidity and cognitive dysfunctions. Notably, COMT is always hemideleted in the affected subjects and the authors present this syndrome as a powerful model for studying the role of COMT in schizophrenia and related cognitive abnormalities. In accordance with this, O'Tuathaigh and colleagues nicely summarize data from clinical studies, mutant mice, and psychopharmacological data related to COMT as a drug target for schizophrenia. Finally, Tucci and colleagues dissect sleep abnormalities as an endophenotype of schizophrenia. In particular, they discuss how COMT might affect sleep and cortical development with relevance to schizophrenia.

Considering its biological functions, there are other neuropsychiatric disorders in which COMT might potentially be implicated. However, fewer primary research studies have investigated these options. In this context, this issue includes two manuscripts that might serve as a primer to encourage further investigation. Serretti and Olgiati present a concise review on the potential role of the COMT gene in Alzheimer's disease pathophysiology. The work presented suggests that future research should focus on the role of COMT in Alzheimer's disease pathogenesis and on the feasibility of targeting COMT activity in its treatment. Similarly, COMT as a modulator of reward processes and its relevance to drug addiction has received scarce attention until now. Tunbridge and coworkers present a balanced overview of COMT as a potential genetic factor implicated in reward processing and possibly addiction-related phenomena that might stimulate new studies on this topic.

COMT DRUG DESIGN

This special issue concludes with a manuscript by Barrow, which provides a useful state-of-the-art overview of COMT inhibitors. This review summarizes the major classes of COMT inhibitors, from early catechol and pyrogallol variants to bisubstrate inhibitors. In particular, it is evident that the nitrocatechol substructure has proven to be a particularly productive scaffold.

In conclusion, the present issue aims to be a useful tool when considering COMT as a potential therapeutic target for the treatment of several disorders of the nervous system. It is becoming increasingly clear that genetic factors may play an important role in the clinical expression of at least some neuropsychiatric disorders and their behavioral symptoms (i.e. cognitive dysfunctions). One of the key points which emerge from this issue is the prospect of developing personalized treatment regimens based on COMT genotype, an idea which is rapidly gaining traction within the health care industry for the administration of pharmaceuticals.

ACKNOWLEDGEMENTS

The Guest Editor would like to thank all of the contributing authors for their excellent review articles, together with Ms. Hina Wahaj and the staff of Bentham Science Publishers for their help in assembling this special issue of the journal.

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