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Editorial

Novel Therapeutic Targets for Older Drugs

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Editorial

The discovery of new drugs is one of the key goals of the pharmaceutical industry as well as academic biomedical research. The cost of drug discovery and development rose markedly during the last three decades and the process is highly time consuming too [1]. The rising cost and time is making the development of new drugs increasingly unaffordable for both pharmaceutical companies and the consumers [2,3]. A strategy to face this crisis could be to identify novel therapeutic effects of FDA approved drugs which are safe and are in human use since long time. Recent technological advances have allowed researchers to identify novel therapeutic use of older drugs and extend their therapeutic use in a cost effective way. These studies performed at the interface of preclinical and clinical research are expected to reduce more than 75% cost while also significantly reducing the time in the drug discovery process.

An additional problem encountered in the discovery of drugs for brain disorders is the lack of appropriate biomarkers and animal models for many of these diseases. Moreover, there is heterogeneity in the symptoms and pathophysiology of brain disorders; and often symptoms of different diseases overlap [4]. The concept of new targets for older drugs would be more useful in the drug discovery for brain disorders because it can reduce not only the cost but also other potential risks intrinsic to the drug.

The Concept of Polypharmacology

The traditional method of drug discovery and development is based on 'one drug one target' model. According to this model, greater selectivity and higher affinity of a drug for a single target can maximize efficacy and reduce side effects. On the other hand, the majority of drugs do not act via single target and pharmacological effects produced by these drugs cannot be explained in terms of 'one drug one target' model. The concept of polypharmacology therefore emerged; according to which a pharmacological agent can produce effects via multiple targets [5]. Although targets other than therapeutic targets are usually thought to be associated with drug side effects, but it is highly likely that many of these can produce therapeutically important effects.

Antidepressants

There are several examples that a novel therapeutic target for a drug was identified while it was in human use in the treatment of entirely different disease. One of the best examples is the prototypical antidepressant compound iproniazid. The antidepressant potential of iproniazid was discovered and monoamine hypothesis of depression proposed [6] based upon evidence that antihypertensive drug reserpine produced depression like effects in patients treated with the drug, while euphoria and hyperactive behavior appeared in patients treated with iproniazid for tuberculosis. Preclinical studies reported that reserpine binds with vesicular uptake sites to inhibit the storage of monoamines. The monoamines not stored in the synaptic vesicles are degraded and a synaptic depletion of monoamine produces depression like effects. Iproniazid was found to inhibit the degradation of monoamines by monoamine oxidase to alleviate reserpine-induced depression in animal models.

Currently, selective serotonin reuptake inhibitors are the most commonly prescribed antidepressants; but up to two thirds of patients with major depression do not respond to the first medication prescribed [7]. Depression is called treatment resistant when antidepressant drugs from at least two different classes fail to produce clinical improvement. Novel approaches with new molecular mechanism, beyond monoamines, are therefore highly needed. In this context, experimental studies performed in our laboratory and also in other laboratories, reviewed in [4,8], show that the peptide hormone produces antidepressant effects in rat models. Because leptin levels are not always smaller in depressed patients, it is suggested that like obesity, depression may also be associated with leptin resistance.

Leptin a peptide hormone is secreted from adipocytes and acts centrally to elicit negative feedback control over energy homeostasis [8]. Although normal or smaller circulating levels of leptin also sometimes occur in obesity, but mostly human obesity is associated with higher levels of circulating leptin [9]. Leptin receptors are also expressed in beta pancreatic cells and leptin inhibits insulin secretion by binding to these receptors [10] suggesting a role of leptin in the regulation of insulin secretion and in the etiology of type 2 diabetes. In addition, preclinical studies [11] as well as human studies [12] show an important role of leptin in cognition. It may be argued that treating leptin resistance can improve therapeutics in depression, obesity as well as cognitive impairment.

Metformin, an Example

Evidence that drugs used for systemic effect can produce therapeutically useful central effects is provided by studies on metformin (1, 1-dimethylbiguanide hydrochloride). The drug launched in 1950's is now widely prescribed for the treatment of type 2 diabetes [13]. It is the drug of choice, recommended by diabetes associations in many counties [14]. It is considered a safe drug largely because it could treat diabetes without causing hypoglycemia or stimulating secretion of insulin. The mechanism by which metformin ameliorates high blood sugar is only partly understood. An Adenosine Monophosphate (AMP) dependent Activation of Protein Kinase (AMPK) is, at present, commonly accepted mechanism [15].

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Because of its safety and efficacy during long term use, there is a growing interest not only in the mechanism by which metformin can treat diabetes, but also in the identification of its potentially novel therapeutic effects [16].

Beyond its effect on glucose metabolism, metformin can cross blood brain barriers to produce central effects [17]. Administration metformin has been shown to improve learning and memory in rats treated with high fat diet and exhibiting insulin resistance [18]. It has been shown in a clinical study that metformin can enhance the recovery of depression comorbid with type 2 diabetes; through improving cognitive performance [19].

Conclusion

In conclusion, the aim of this editorial is to introduce concept of polypharmacology in discovering novel therapeutic targets of older drugs which are safe and have been in human use since long time. These investigations may lead to drug discovery in a time and cost effective way, beneficial for both the pharmaceutical industry, researchers and the consumers.

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