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Antibiotic resistance breakers: Can we reverse antibiotic resistance?

[1]Suvidhi, [1*]Sudesh Kumar, [2]Taruna Bhati, [3]Nasrul I. Shaikh
[1]Senior Research Fellow, ICAR-National Research Centre on Equines, Hisar, Haryana, 125001, India
[2]Assistant Professor, Department of Veterinary Microbiology and Biotechnology, College of Veterinary and Animal Science, Bikaner, Rajasthan, 334001, India
[3]Senior Scientist Biotechnology, All Vet Diagnostic Solutions PVT LTD, Delhi, 110016, India
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Abstract

Antibiotic resistance is increasing at an alarming rate and is now widely recognized as a global issue that requires urgent attention. In order to mitigate antibiotic resistance, a new strategy to increase antibiotic potency and reverse drug resistance is needed. Antibiotic resistance typically induces a fitness cost that shapes the fate of antibiotic-resistant bacterial populations. However, the cost of resistance can be mitigated by compensatory mutations elsewhere in the genome, and therefore the loss of resistance may proceed too slowly to be of practical importance. Despite several strategies being deployed, resistance levels are still of huge concern, and antibiotic resistance breakers (ARBs) represent a promising avenue of research to counter this.

Introduction

Antibiotic resistance is one of the biggest threats to global health, food security, and development today. Antibiotic resistance can affect anyone, of any age, in any country. Antibiotic resistance occurs naturally, but misuse of antibiotics in humans and animals is accelerating the process.

Bacteria, not humans or animals, become antibiotic-resistant. These bacteria may infect humans and animals, and the infections they cause are harder to treat than those caused by non-resistant bacteria.

The effects of antibacterial resistance are not limited to those patients who develop bacterial infections; wider medical procedures stand to be impacted. Antibiotic prophylaxis is commonly employed to avoid the development of infections, both preoperatively for a variety of surgical procedures and for immunocompromised patients undergoing chemotherapy. Such prophylactic measures will no longer be

possible if AMR spreads at its current rate, which could in turn impact the scope of surgical procedures available to clinicians and the quality of patients' lives.

Infections of antibiotic-resistant pathogens pose an ever-increasing threat to mankind. The investigation of novel approaches for tackling the antimicrobial resistance crisis must be part of any global response to this problem if an untimely reversion to the pre-penicillin era of medicine is to be avoided. One such promising avenue of research involves so-called antibiotic resistance breakers (ARBs), capable of re-sensitizing resistant bacteria to antibiotics.

To tackle the increasing emergence of AMR, alternative treatment strategies have been designed with the collective aim of reducing the number of antibiotics used and preserving the current classes of antibiotic for further clinical use. This review aims to showcase the potential of one such strategy, the use of antibiotic resistance breakers (ARBs). These are compounds that can increase the effectiveness of current antibiotics by combatting the resistance mechanisms employed against them. ARBs may or may not have direct antibacterial effects and can either be co-administered with or conjugated to failing antibiotics. Though ARBs have previously been referred to as antibiotic adjuvants, the latter also refers to alternative treatments such as drugs which stimulate host defense mechanisms to aid the eradication of bacterial infections.

The major classes of ARBs currently under investigation include modifying-enzyme inhibitors, membrane permeabilizers' and efflux pump inhibitors (EPIs).

Modifying enzyme inhibitors

Bacteria employ a diverse range of enzymes to modify or destroy antibiotics in order to render them ineffective and achieve a resistant phenotype. These enzymes can be categorized by both their mechanisms of action and their substrate antibiotics. Hydrolysis of certain susceptible bonds within the antibiotic molecule, transfer of a functional group to the antibiotic and (less commonly) the actions of redox and lyase enzymes are all examples of detoxification mechanisms. This led to the development of antibiotics that would tolerate their actions, such as the β-lactam flucloxacillin which was designed to tolerate the action of the penicillinases. A method which has found more success is the design of modifying enzyme inhibitors, a term which encompasses the wide variety of chemical compounds that target bacterial enzymes involved in antibiotic modification and destruction. Modifying enzyme inhibitors are used to disrupt bacterial detoxification enzymes, increasing the effectiveness of a co-administered antibiotic. Two major classes are the BLIs and aminoglycoside-modifying enzymes.

Membrane permeabilizers

Gram-negative bacteria are intrinsically resistant to several antibiotic classes because of the presence of a second, outer membrane compared to Gram-positive bacteria which these antibiotics cannot penetrate. The Gram-negative bacterial envelope consists of three components; an inner membrane which surrounds the organelles, an outer membrane and a periplasmic region between the two membranes containing a peptidoglycan layer. The outer membrane contains porins, water-filled protein channels that facilitate entry of hydrophilic molecules into the bacterial cell; mutations in Gram-negative bacteria resulting in reduced porin expression can reduce influx of hydrophilic drugs into these bacteria. This method of antibacterial resistance has been confirmed in several clinically relevant bacterial species, such as *P. aeruginosa*. Besides directly damaging the cell membrane, various other methods have been suggested to increase rates of antibiotic influx in bacterial cells, such as the use of liposomal drug preparations. However, it is the use of membrane permeabilizers, compounds that make the Gram-negative outer membrane more permeable to facilitate increased antibiotic influx that will be reviewed herein. Membrane permeabilizers can function by chelating and removing divalent cations from the outer membrane and/or (in the case of permeabilizers with a net cationic charge) associating with the negatively charged outer membrane to disrupt it, causing a breakdown of outer membrane structure. The effectiveness of putative membrane permeabilizers can be assessed by measuring the level of uptake of substances that would not normally be able to penetrate the Gram-negative outer membrane, such as a hydrophobic probe. The fluorescent dye N-phenyl-1-napthylamine (NPN) is used for this purpose; an increase in fluorescence indicates increased incorporation of NPN into the outer membrane of the pathogen and thus increased outer membrane permeability. Besides enabling increased influx of antibiotics, membrane permeabilization alone can be sufficient to cause bacterial lysis; as such, several of the compounds mentioned in this section also have direct antibacterial activity.

Efflux pump inhibitors

Bacterial efflux pumps act to decrease intracellular concentrations of antibiotics by pumping antibiotics out of bacterial cells, thereby reducing their effectiveness. The presence of efflux systems has been confirmed in prokaryotic species, archaea and both inferior and superior eukaryotic species. Their main function is the extrusion of undesirable compounds from cells; these include heavy metals, organic solvents, dyes such as ethidium bromide, amphiphilic detergents, biocides, quorum sensing molecules and metabolites in addition to antibiotics. The presence of efflux pumps and their clinical significance in

contributing towards AMR has been confirmed in many bacteria, including *M. tuberculosis* and *P. aeruginosa*.

Conclusion

Ultimately, treating resistance will require a portfolio of strategies including antibiotic resistance breakers, drug discovery, resistance monitoring, and combinations of novel methods to invert the selection for resistance.

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