J Cell Immunol. 2023;5(3):87-91.

Journal of Cellular Immunology Commentary

Fluoxetine is Antimicrobial and Modulates the Antibiotic Resistance Status of Bacteria

Alison M Mackay[1,2,*]

[1]Flex Clin Sci Ltd, Salford, UK

[2]Faculty of Biology, Medicine and Health, The University of Manchester, UK

*Correspondence should be addressed to Alison M Mackay, ynfdwas1@gmail.com

Received date: July 28, 2023, **Accepted date:** September 25, 2023

Citation: Mackay AM. Fluoxetine is Antimicrobial and Modulates the Antibiotic Resistance Status of Bacteria. J Cell Immunol. 2023;5(3):87-91.

Keywords: Microbial resistance, Efflux pump inhibitors, Selective serotonin reuptake inhibitors, Innate immunity, Nosocomial infection, Catheter-associated urinary tract infection

Commentary

The ability of mobile genetic elements to transfer drug resistance between bacteria can cause the rapid establishment of multi-drug resistance (MDR) [1,2], and human infection caused by multi-resistant, rather than susceptible organisms increases the likelihood of death [3]. Such antibiotic resistance will be the cause of millions of premature deaths and the loss of millions of pounds to the global economy [4].

Nosocomial strains of *Staphylococcus pyogenes* (*S. pyogenes*) resistant to penicillin were reported in 1947 with a mixture of resistant and sensitive strains in the same patient [5]. Within a decade, 70% of infections in one hospital were resistant to at least two antibiotics, however, a policy for prescribing them facilitated susceptibility to penicillin in 50% within a year, cutting prevalence of infection by a third [6]. From this it can be surmised that in a third of patients, antibiotic-susceptible *S. pyogenes* persisted following treatment.

The innate immune system of humans relies on pattern recognition receptors (PRRs) recognising endogenous and exogenous molecular patterns related to pathogens [7]. Toll-like receptors (TLR) function as transmembrane PRRs and release inflammatory cytokines, interferons (IFNs), and antimicrobial peptides (AMPs) on engagement. Excessive signalling of TLR4s plays a significant role in Sepsis, proven when TLR4 knock-out mice were unaffected by lethal doses of Lipopolysaccharides (LPS) [8,9].

The term 'inflammasome' describes an intracellular cytoplasmic multiprotein complex with a pathogen recognition receptor [10] including NOD-like Receptors (NLRs) and pyrins which are specifically triggered by ligands. The canonical inflammasome is the part of the intracellular innate immunity that was observed first. It comprised the formation of pores in the cell membrane, followed by the release of caspase 1, then IL-1β and pro-IL18. The non-canonical inflammasome releases Caspase 4 and 5 which act as both sensor to pathogens, and effector in the release of IL-1β, IL-18 and events of pyropoptosis. Another non-canonical pathway has been observed in mice and uses Caspase 11 on exposure to LPS and other toxins [11-13].

Minimum Inhibitory Concentration (MIC) defines levels of susceptibility or resistance of specific bacterial strains to treatment [14]. More specifically, it is the lowest concentration of an antimicrobial (mg/ml) which prevents growth of a test strain of an organism *in vitro*. The antibiotic resistance status and MICS of a range of microbes can be found on the EUCAST website [15]. The technique comprises the distribution of a specific antibiotic over a petridish and the seeding of a bacterial species on the right-hand side; the leftward proliferation of the microbe suggests it has some resistance to the drug concentration present.

The selective serotonin reuptake inhibitors (SSRIs) have an

antibacterial effect when used alone [16]. Additionally, the innate bacterial efflux pumps that can prematurely decrease the intracellular concentration of antibiotics, are blocked by efflux pump inhibitors (EPI's) like Fluoxetine [17], allowing the medicine to act for longer. However, augmentation of antibiotics by this particular drug depends heavily on dose and regimen [18].

Proteus mirabilis is frequently found in catheter associated urinary tract infection (CAUTI) and is associated with serious clinical complications given its ability to form biofilms on even state-of-the-art indwelling catheters [18]. *In vitro*, a MIC of 0.26 mg/ml of fluoxetine was found for *P. miribilis* B4. *In vivo*, reduced blockage and lower levels of bacteria in residual bladder urine were found using small doses of the drug [18].

When taken alongside sub-inhibitory levels of three different antibiotics, a similar dose of fluoxetine was able to control *E. coli*, *P. aeruginosa*, and *S. aureus* [19]. Conversely, when a petridish of agar was exposed to this small dose of fluoxetine for 30 days prior to *E. coli* seeding, huge increases in the MIC of three different antibiotics were observed [20]. This study also revealed four different modes of antibiotic efflux and concluded that up-regulation of pumps was caused by ROS-mediated mutagenesis of DNA-binding transcriptional regulators. A lab study of three different antibiotics treating *Acinebacter baumanni* showed that 30 days prior exposure to fluoxetine also caused Ciprofloxacin resistance given this increase in efflux. Colistin-resistance occurred by a different mechanism, and the status of the antibiotic imipenem did not change [21]. So as a general statement we can say that a patient's prior exposure to fluoxetine is likely to increase their required dose of antibiotics for bacterial infection.

It is known that the use of antibiotics at sub-inhibitory levels is a cause of antibiotic resistance [22], and we have highlighted here that parallel micro-dosing of SSRIs negates this. Obviously, a patient's co-morbidity, BMI, and regular medications would also be influential. All modes of resistance are transient [23] and so close monitoring of patient's would allow optimisation of the dose and timing of antibiotics and adjunct drugs.

Successful antibacterial activity has been demonstrated in the lab and in patients with indwelling catheters for Fluoxetine used alone, and at micro-doses alongside low-dose antibiotics. A range of common medications with antimicrobial properties are summarised in **Table 1**, often working symbiotically with antibiotics. Alternatively, potentiation of the innate immune system could prevent or fight infection at an even earlier stage, so long as the risk of sepsis is mitigated. To put these conclusions in context, WHO have stated that carbapenem resistance in *A. baumanni, P. aeruginosa and Enterobacteria* are now a critical priority, with antibiotic resistant *S. aureus* making the 'high priority' list [24].

Acknowledgements

Thank you to my parents for continued support. Also thank you to Ruth Garry for life coaching, and bro-in-law Mike Roberts for helping me with DIY tasks on his rare days off.

References

1. Baquero F, Martínez JL, F Lanza V, Rodríguez-Beltrán J, Galán JC, et al. Evolutionary Pathways and Trajectories in 1. Antibiotic Resistance. Clin Microbiol Rev. 2021;34(4):e0005019.

2. McMillan EA, Gupta SK, Williams LE, Jové T, Hiott LM, Woodley TA, et al. Antimicrobial Resistance Genes, Cassettes, and Plasmids Present in *Salmonella enterica* Associated with United States Food Animals. Front Microbiol. 2019;10:832.

3. Cosgrove SE. Evidence that prevention makes cents: Costs of catheter-associated bloodstream infections in the intensive care unit. Crit Care Med. 2006;34(8):2243-2244.

4. O'Neill J. Tackling Drug-resistant infections globally: Final Report and Recommendations. AMR Review 2016.

5. Barber M. Staphylococcal infection due to penicillin-resistant strains. Br Med J.1947;2(4534):863-865.

6. Barber M, Dutton AA, Beard MA, Elmes PC, Williams S R. Reversal of antibiotic resistance in hospital Staphylococcal infection. Br Med J. 1960;1(5165):11-17.

7. Downs KP, Nguyen H, Dorfleutner A, Stehlik C. An overview of the non-canonical inflammasome. Mol Aspects Med. 2020;76:100924.

8. Hoshino K, Takeuchi O, Kawai T, Sanjo H, Ogawa T, Takeda Y, et al. Cutting edge: Toll-like receptor 4 (TLR4)deficient mice are hyporesponsive to lipopolysaccharide: evidence for TLR4 as the Lps gene product. J Immunol. 1999;162(7):3749-3752.

9. Poltorak A, He X, Smirnova I, Liu MY, Van Huffel C, Du X, et al. Defective LPS signaling in C3H/HeJ and C57BL/10ScCr mice: mutations in Tlr4 gene. Science. 1998;282(5396):2085-2088.

10. Broz P, Dixit VM. Inflammasomes: mechanism of assembly, regulation and signalling. Nat Rev Immunol. 2016;16(7):407-420.

11. Young-Su Y. Role of Caspase-11 Non-Canonical Inflammasome in Macrophage-Mediated Inflammatory Responses. Int J Immunol Immunother. 2018;5:034.

12. Kayagaki N, Warming S, Lamkanfi M, Vande Walle L, Louie S, Dong J, et al. Non-canonical inflammasome activation targets caspase-11. Nature. 2011;479(7371):117-121.

13. Shi J, Zhao Y, Wang Y, Gao W, Ding J, Li P, et al. Inflammatory caspases are innate immune receptors for intracellular LPS. Nature. 2014;514(7521):187-192.

14. Kowalska-Krochmal B, Dudek-Wicher R. The Minimum Inhibitory Concentration of Antibiotics: Methods, Interpretation, Clinical Relevance. Pathogens. 2021;10(2):165.

Drug Dose (mg/ml)	Molecular Formula	Molecular Weight (g/mol)	Ionisation	Water Solubility (mg/L at 25°C)	Lipophillic	Standalone Capability	Effect in Combination with Antibiotics (abx)	Ref.
Fluoxetine 0.26 (flx)	$C_{17}H_{18}F_3NO$	309.33	+ve	No	Yes	Indwelling Catheter Users. *P. mirabilis* MIC 0.26 mg/ml		[18]
							Lab Study of successful treatment of bacteria alongside abx under their normal minimum inhibitory dose. *E. coli, P. aeruginosa, S. aureus*	[19]
							Lab study requiring abx above their normal inhibitory dose after 30 days of fluoxetine. *S. aureus*	[20]
							Lab study resulting in increasing MIC for abx *A. baumanni* flx for 30 days, followed by: Ciproflaxacin >MIC	[21]
Acetylsalicylic acid/Salicylic Acid	$C_7H_6O_3$	138.12	-ve	2240	yes	Inhibition of *Campylobacter pylori, Helicobacter pylori, Epidermophyton floccosum, Microsporum* spp, *Trichophyton* spp.	Increases the antimicrobial susceptibility of many pathogens, but decreases the effect of aminoglycosides, beta-lactams and fluoroquinolones	[25-31]
Paracetamol	$C_8H_9NO_2$	151.16	+ve	14000	yes		Induction of beta-lactamase activity in *Serratia marcesens*	[32]

Ibuprofen	$C_{13}H_{18}O_2$	206.29	+ve	21	yes	Inhibits *E. coli, S. aureus, Trichophytan spp, Microsporun spp*	Reduce the effect of azithromycin and moxifloxacin in humans	[33-36]
Diclofenac	$C_{14}H_{11}Cl_2NO_2$	2.96	+ve	9	yes	Inhibits *E. coli*		[35]
Sargassum Polyceratium extracts; Sp-1 (13^2-hydroxy-(13^2-R) pheophypin-a; 13^2-hydroxy-(13^2-S) pheophytin-a						Lab study of three biocidal agents against *S. aureus* showed no effect.	Lab study of antibiotic and three strains of *S. aureus*. The presence of biocidal agents resulted in a four-fold reduction in microbial resistance to antibiotics.	[36,37]
Duloxetine 0.20	$C_{18}H_{19}NOS$	297.4	+ve	3	Yes	Lab study resulting in successful treatment of: *S. aureus, E. coli, Candida albicans, Bifidobacterium, E. faecalis, Lactobacillus rhamnosus*		[38,39]
Venlafaxine 0.20	$C_{17}H_{28}ClNO_2$	313.9	+ve	267	Yes			
Fluvoxamine 0.20	$C_{15}H_{21}F_3N_2O_2$	318.33	+ve	4340	Yes			
Escitalopram 0.20	$C_{20}H_{21}FN_2O$	324.40	+ve	31.09	Yes			
Mirtazapine 0.20	$C_{17}H_{19}N_3$	265.35	+ve	slightly	Yes			
Fluoxetine/ 0.20	$C_{17}H_{18}F_3NO$	309.33	+ve	No	Yes			
Desipramine/ 0.00-0.80	$C_{18}H_{22}N_2$	266.4	+ve	56.8	Yes	*Lab study of treatment success proportional to dose:* *B. animalis, B. fragilis, F. prausnitzii*		
Aripiprazole/ 0.00-0.80	$C_{23}H_{27}Cl_2N_3O_2$	448.4	+ve	Slightly	Yes			

15. European Committee on Antimicrobial Susceptibility Testing. 2023. Clinical Breakpoints and dosing of Antibiotics.27/07/2023. {https://www.eucast.org/clinical_breakpoints}.

16. Karine de Sousa A, Rocha JE, Gonçalves de Souza T, Sampaio de Freitas T, Ribeiro Filho J, Melo Coutinho HD. New roles of fluoxetine in pharmacology: Antibacterial effect and modulation of antibiotic activity. Microb Pathog. 2018;123:368-371.

17. Nzakizwanayo J, Scavone P, Jamshidi S, Hawthorne JA, Pelling H, Dedi C, et al. Fluoxetine and thioridazine inhibit efflux and attenuate crystalline biofilm formation by *Proteus mirabilis*. Sci Rep. 2017;7(1):12222.

18. Jin M, Lu J, Chen Z, Nguyen SH, Mao L, Li J,et al. Antidepressant fluoxetine induces multiple antibiotics resistance in *Escherichia coli* via ROS-mediated mutagenesis. Environ Int. 2018;120:421-430.

19. Dos Santos SBF, Pereira SA, Rodrigues FAM, da Silva ACC, de Almeida RR, Sousa ACC, et al. Antibacterial activity of fluoxetine-loaded starch nanocapsules. Int J Biol Macromol. 2020;164:2813-2817.

20. Laws M, Shaaban A, Rahman KM. Antibiotic resistance breakers: current approaches and future directions. FEMS Microbiol Rev. 2019;43(5):490-516.

21. Gurpinar SS, Kart D, Eryilmaz M. The effects of antidepressants fluoxetine, sertraline, and amitriptyline on the development of antibiotic resistance in *Acinetobacter baumannii*. Arch Microbiol. 2022 Mar 30;204(4):230.

22. Mackay AM. The evolution of clinical guidelines for antimicrobial photodynamic therapy of skin. Photochem Photobiol Sci. 2022;21(3):385-395.

23. Depardieu F, Podglajen I, Leclercq R, Collatz E, Courvalin P. Modes and modulations of antibiotic resistance gene expression. Clin Microbiol Rev. 2007;20(1):79-114.

24. Venter H. Reversing resistance to counter antimicrobial resistance in the World Health Organisation's critical priority of most dangerous pathogens. Biosci Rep. 2019;39(4):BSR20180474.

25. Caselli M, Pazzi P, LaCorte R, Aleotti A, Trevisani L, Stabellini G. Campylobacter-like organisms, nonsteroidal anti-inflammatory drugs and gastric lesions in patients with rheumatoid arthritis. Digestion. 1989;44:101-104.

26. Wang WH, Wong WM, Dailidiene D, Berg DE, Gu Q, Lai KC, et al. Aspirin inhibits the growth of *Helicobacter pylori* and enhances its susceptibility to antimicrobial agents. Gut. 2003; 52:490-495.

27. Ma D, Cook DN, Alberti M, Pon NG, Nikaido H, Hearst JE. Genes acrA and acrB encode a stress-induced efflux system of *Escherichia coli*. Mol Microbiol. 1995; 16:45-55.

28. Ma H-X, Wang W-H, Hu F-L, Li J. Effect of aspirin and celecoxib on *Helicobacter pylori in vitro*. Shijie Huaren Xiaohua Zazhi. 2005; 14:2747-2752.

29. Domenico P, Schwartz S, Cunha BA. Reduction of capsular polysaccharide production in *Klebsiella pneumoniae* by sodium salicylate. Infect Immun. 1989; 57:3778-3782.

30. Chowdhury B, Adak M, Bose SK. Flurbiprofen, a unique non-steroidal anti-inflammatory drug with antimicrobial activity against *Trichophyton*, *Microsporum* and *Epidermophyton* species. Lett Appl Microbiol. 2003;37:158-161.

31. Zimmermann P, Curtis N. Antimicrobial Effects of Antipyretics. Antimicrobial Agents and Chemotherapy. 2017;61(4): e02268-16.

32. Puig M, Palomar J, Loren JG, Vinas M. Modification by analgesics of the susceptibility to antibiotics in *Serratia marcescens*. New Microbiol. 1995;18:385-390.

33. Sanyal AK, Roy D, Chowdhury B, Banerjee AB. Ibuprofen, a unique anti-inflammatory compound with antifungal activity against dermatophytes. Lett Appl Microbiol. 1993;17:109-111.

34. Drago L, De Vecchi E, Nicola L, Valli M, Gismondo MR. Effects of subinhibitory concentrations of ibuprofen isobuthanolammonium on virulence factors of uropathogenic *Escherichia coli*. J Chemother. 2005;14:314-315.

35. Mazumdar K, Dutta NK, Dastidar SG, Motohashi N, Shirataki Y. Diclofenac in the management of E. coli urinary tract infections. In Vivo. 2006;20:613-619.

36. Menezes-Silva S, Lira NS, Mangueira do Nascimento Y, Araújo Ramos Meireles R, da Silva Dias C, et al. Modulation of drug resistance in *Staphylococcus aureus* by 132-hydroxy-(132-R/S)-pheophytin isolated from *Sargassum polyceratium*. Microbial Pathogenesis. 2020;141:104034.

37. Borbón H, Herrera JM, Calvo M, Trimiño H, Sierra L, Soto R, et al. Antimicrobial Activity of Most Abundant Marine Macroalgae of the Caribbean Coast of Costa Rica. Journal of Asian Scientific Research. 2012;2(5):292-299.

38. Rukavishnikov G, Leonova L, Kasyanov E, Leonov V, Neznanov N, Mazo G. Antimicrobial activity of antidepressants on normal gut microbiota: Results of the in vitro study. Frontiers in Behavioral Neuroscience. 2023;17:1132127.

39. Chait, YA. et al. Unravelling the antimicrobial action of antidepressants on gut commensal microbes. Scientific Reports 2020; 10:17878.