

Antidepressants Enhance Host-Resistance in the Body

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Abstract

A review of scientific literature indicates that the use of antidepressants can be generalized to all forms of stress and inflammation as an adjunctive therapy that enhances host resistance. The effects of antidepressants on mood are well-documented through their emotional, cognitive, and behavioral impacts, but these effects do not fully explain their cellular actions. Antidepressants exert trophic effects on cells, inducing neurogenesis and synaptic connectivity. These trophic effects are highlighted in studies showing that antidepressants increase survival in cells, animals, and humans, as well as promote stem cell proliferation. In both depressed patients and animal models of depression, antidepressants reduce the perception of danger (mood effects). The acid sphingomyelinase (ASM) theory offers a more comprehensive explanation than the monoamine theory for the cellular effects of antidepressants. On a cellular level, antidepressants reduce ceramide production by functionally inhibiting the ASM enzyme. This leads cells toward a state that enhances survival, cyto-protection (cyto-resistance), cell reproduction, and mood improvement. This article reviews studies demonstrating that antidepressants increase host resistance to infections, immunological conflicts, stress, and depression. These findings support the use of antidepressants to enhance host resistance in cases of infections, vaccinations, cell damage, stress, depression, and aging.

Keywords: antidepressant, acid sphingomyelinase enzyme, immunity, infection, stress.

INCREASE MOOD WITH ANTIDEPRESSANTS

In this article, we consider all commercially available antidepressants. We understand that all antidepressants are similarly effective in treating depression. Head-to-head trials of 21 antidepressants versus placebo in major depressive disorder (MDD) show odds ratios ranging from 2.13 (95% credible interval 1.89–2.41) for amitriptyline to 1.37 (95% credible interval 1.16–1.63) for reboxetine (1 with 21 antidepressants). All antidepressants share the same mechanism of action on mood, regardless of their initial interactions with monoamines or their adverse effects. The effect of antidepressants on mood remains a subject of scientific debate. Efficacy is observed clinically (mood improvement) and through depression scales. At the cellular level, antidepressants direct cells towards in direction of life, promoting reproduction, cyto-protection, and survival. These are the key markers of the antidepressant effect at the cellular level. All antidepressants (oral or intravenous) enter the bloodstream and reach nearly all cells in the

body. The change in mood is observable across the emotional (reducing sadness, fear, and disgust), cognitive (improving memory and learning), and behavioral (reducing psychomotor retardation and anxiety) dimensions. At the cellular level, mood improvement is linked with a neurotrophic state (increased neurogenesis and synaptic connectivity). Antidepressants elevate mood and promote a trophic state in cells. This trophic state involves increased cell reproduction (e.g., neurogenesis), enhanced cell resistance (e.g., cyto-protection), and improved survival (against toxic and infectious diseases).

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Antidepressant-like effects are evident in animal studies (rats, mice) 20 minutes after administration (i.p.), and behavioral changes can be detected in humans within two hours after an antidepressant injection. Participants administered citalopram exhibit greater prosocial behaviors, enhanced positive recall, and increased positive learning regarding social evaluations of others (2). According to the Zurich meta-analyses, antidepressants show a significant effect of tricyclic antidepressant (TCA) on mood, compared to placebo, after just five days of treatment (3). A naturalistic study of 4,771 depressed patients found a one-point improvement on the Clinical Global Improvement Scale after only one week of mirtazapine (30 mg/D). Treatment was reported to decrease the global Montgomery-Asberg Depression Rating Scale (MADRS) scores by 2.5% per day during the first two weeks, and at a slower rate of 0.5% per day from weeks 2 to 6 (4). This suggests that most antidepressant-induced mood changes at least for TCA (3) and mirtazapine (4) within the first two weeks of treatment. These findings contrast with the common assertion that antidepressants take two weeks to start working. This delay is partly due to the lack of observation in clinical trials before two weeks, and partly because the definition of “delay of action” refers to the time needed for clinicians to observe a clinical improvement in mood. In the mirtazapine study (4), the one-point improvement on the Clinical Global Impression

scale corresponds to a 15% reduction in the MADRS scale, a small change not easy to detect which explain why clinicians need two weeks to detect those changes clinically. While antidepressants may start acting pharmacologically immediately, patients typically feel the effects within a week. The primary antidepressant effect on mood is the reduction of perceived fear. Depressed patients may resist this reduction in fear through ruminations, which activate the brain’s representation of fear and hinder antidepressant effects. Patients who are non-responsive to antidepressants often experience ongoing catastrophic stress (e.g., unemployment) or intense ruminations with rigid, negative thoughts and images.

INCREASE HOST RESISTANCE WITH ANTIDEPRESSANTS

Increase Survival with Antidepressants

The improvement in survival observed in animals treated with antidepressants during viral infections (with fluoxetine, 5), bacterial infections (with amoxapine, 6), or lipopolysaccharide shock (LPS). (with desipramine and fluoxetine, 7) further supports this finding. In humans, antidepressant treatment has been linked to improved survival rates during COVID-19 infection (with fluoxetine, paroxetine, escitalopram, venlafaxine, mirtazapine, 8; with fluvoxamine, 9; with fluvoxamine, 10; with fluvoxamine, 11; with fluoxetine, fluvoxamine, 12; with fluvoxamine,

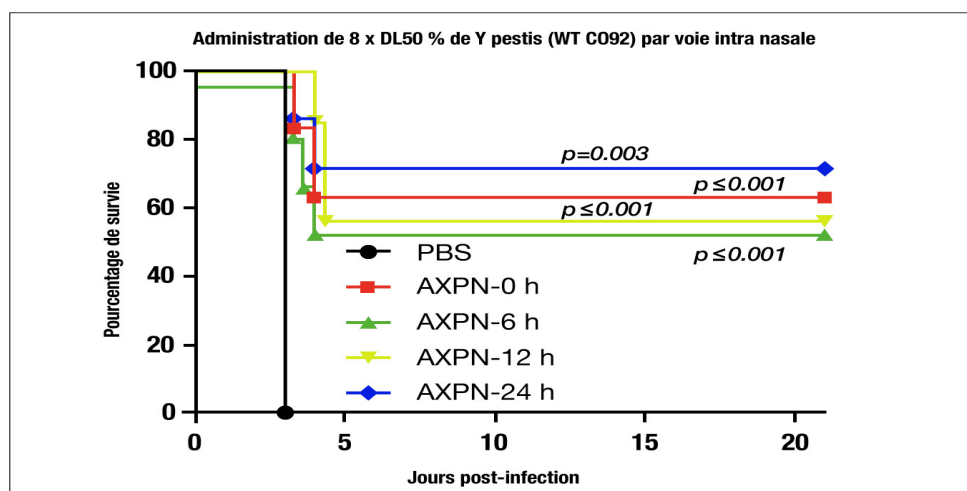


Figure 1. Survival analysis of mice infected with *Y. Pestis* (strain WT CO92) and treated with amoxapine (AXPN). Mice are infected with 8 lethal doses 50% (1 lethal dose 50% = 500 CFU) intranasally. 4 Amoxapine treatments (3 mg/Kg; n=7) are administered intraperitoneally for 3 days at 24-hours intervals. These treatments start at the time of infection (axpn-0), 6H after infection (axpn-6), 12H after infection (axpn-12), and 24H after infection (axpn-24). The control group receives phosphate-buffered saline (PBS; n=5). The data were analyzed using Kaplan-Meier for significance to compare the amoxapine group to the control group. Adapted from Andersson et al., 2017; Combating Multidrug-Resistant Pathogens with Host-Directed Nonantibiotic Therapeutics

13; with fluoxetine, trazodone, 14; with citalopram, paroxetine, 15; with selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), mirtazapine, 16; observational study with fluoxetine, fluvoxamine, escitalopram, amitriptyline, and others medications functionally inhibiting the acid sphingomyelinase/ceramide system (named FIASMA psychotropic medications), 17; with 22 different antidepressants, 18). Patients treated with antidepressants exhibited reduced deterioration and lower mortality rates compared to those who were not treated. In rats infected with SARS-CoV-2, fluoxetine replicated the antiviral and anti-inflammatory effects seen in humans (19). In animal studies, mice treated with antidepressants after exposure to a lethal dose of bubonic plague demonstrated a significantly higher survival rate (>50% surviving at day 21) compared to untreated mice (all died within four days). The authors confirmed that antidepressants did not have a direct bactericidal effect (6).

Further studies, such as those involving desipramine and fluoxetine during LPS exposure in mice, show that antidepressants increase survival rates compared to untreated controls. (20) These findings suggest a substantial survival benefit (40-60% increase in survival) from antidepressants during infections. This benefit is consistent across viral (with amitriptyline, 21; with antidepressants in patients, 22), bacterial (with amitriptyline, 23; with amitriptyline, 24; with fluvoxamine, 25), parasitic (with desipramine, 26), and fungal infections (with sertraline, 27; with sertraline, 28; with fluoxetine, 29). Reduced lesions are also observed in all forms of inflammation, including autoimmune disorders (with amitriptyline, 30; with fluoxetine, 31; with phenelzine, 32; with St John's Wort, hyperforin, 33; with imipramine, 34; with clomipramine, 35; with paroxetine, 36; with amitriptyline, 37; with zimeldine, clomipramine, imipramine, maprotiline, 38), toxic aggression (with mirtazapine, 39 traumatic injuries (with amitriptyline, 40), spinal cord injury (with fluoxetine, 41, 42), wound healing (with fluoxetine, 43), and burns (with citalopram, 44). Antidepressants reduce inflammation and promote an anti-inflammatory effect both in depression and during infections (with amitriptyline, 45; with doxepin, 46; with desipramine, fluoxetine, 47; with vortioxetine, 48). They also reduce pro-inflammatory cytokines while increasing anti-inflammatory cytokines (49, meta-analysis with antidepressants, 50). In immune cells, antidepressants induce an anti-inflammatory state in macrophages (with

monoamine reuptake inhibitors, lithium, valproate, agomelatine, tianeptine, electroconvulsive shock, and vagus nerve stimulation, 51; with ketamine, 52). These powerful anti-inflammatory effects protect the host during infection.

Cells Replication

The proliferative effect of antidepressants is both obvious and neglected. It is obvious because all antidepressants enhance neurogenesis by inducing neuronal stem cell proliferation (with SSRI, TCA, MAO inhibitors, 53). However, it is neglected because antidepressants not only enhance neuronal stem cells but they also augment stem cell proliferation in autologous stem cells (with desipramine, 54), adipose-derived stem cells (with fluoxetine, 55), and endometrial stem cells (with citalopram, 56). Adding an antidepressant to a mesenchymal stem cell culture increases cell proliferation. Thirty days of impregnation with sertraline and retinoic acid provide a 7.41 population doubling, whereas without sertraline, the population doubling is only 5.63 (with sertraline, 57). Since immune cells are produced from hematopoietic stem cells in the bone marrow, increased production of immune cells should enhance immune system efficacy. Antidepressants have been shown to increase the efficacy of vaccination with the zoster vaccine (with and without antidepressant treatments, 58). The proliferative effect of antidepressants affects neurons, the immune system cells, and possibly all cells in the body.

Increase in Cell Protection

The revolutionary aspect of this discovery lies in the demonstration that antidepressants protect cell cultures from dying. It is not merely the fact that antidepressants increase host resistance that is astonishing, but rather that they protect cells at the cellular level. In non-neural cells, no neurotransmission is involved in producing this effect. Antidepressants directly protect cells from toxic assaults (with desipramine, fluoxetine, moclobemide, 59). In a cell culture model subjected to high and toxic concentrations of corticosteroids, desipramine (0.625-10 micromol/L), fluoxetine (0.625-10 micromol/L), and moclobemide (2.5-40 micromol/L) exhibit cyto-protective effects. This cyto-protective effect is also observed in vivo with mood regulators: lithium (lithium chloride and lithium carbonate) reduces the damage caused by streptozotocin in a rat model of diabetes, exerting a cytoprotective action on pancreatic β -cells and attenuating oxidative stress damage (60). This cyto-protective effect is also

seen on open wounds (with topical fluoxetine, 61; with amitriptyline-based biodegradable PEG-PLGA self-assembler nanoparticles, 62; with fluoxetine gel of solid lipid nanoparticles, 63; with topical fluoxetine, 64) and in the topical treatment of these wounds in humans (with hypericum perforatum, 65).

However, this cyto-protective effect could be detrimental in cases requiring immunosuppression, such as kidney allogeneic grafts (with and without the use of antidepressants before transplantation, 66). In some cases, antidepressants could benefit from both parties in an immune conflict: the host and the cancer cells or the host and blood parasites. For instance, antidepressants could boost the host immune system while also promoting cancer cell proliferation if cancer has already begun. Studies in oncology show conflicting results: antidepressants can both prevent and promote cancer (with and without antidepressant treatment, 67). On one hand, antidepressants protect populations from developing cancer; on the other hand, antidepressants promote cancer proliferation if the cancer has started.

The Acid Sphingomyelinase (ASM) theory best explains this cyto-protective finding. The ASM enzyme generates ceramide, and ceramide accumulation induces mitochondrial and cell membrane damage and apoptosis. Antidepressants inhibit the ASM enzyme, protecting cells from dying. All types of antidepressants (IMAO, SSRI, TCA) functionally inhibit the ASM enzyme, in or on the cells. (with amitriptyline, fluoxetine, 68; with tricyclic antidepressants, 69).

DISCUSSION

Antidepressants simultaneously increase host resistance in the body and improve mood in the brain. We propose to generalize the effect of antidepressants on mood to an increase host-resistance in the whole body. Antidepressants drive the cells toward trophic effects.

Clinical background: Antidepressants Increase Host Resistance

Today, antidepressants are used to enhance host resistance against herpes virus infection (70 with amitriptyline, nortriptyline, desipramine). The common belief is that antidepressants reduce infection-related pain by acting on neurotransmission. However, it is not usually understood how antidepressants help patients control the infection itself, possibly by reducing ceramide accumulation in the host (with amitriptyline, 71). We

propose that antidepressants augment host resistance to stress, and this effect can be generalized to all forms of stress, such as infections, toxic aggressions, and aging (with deprenyl, 72). We argue for using antidepressants as adjunctive therapy to enhance host resistance in a wide range of diseases, especially in older people.

Effects of Age

In the immune system, as in mood, we expect that aged and depressed patients will benefit from antidepressants more than young and healthy subjects. During COVID-19 infection, death rates were primarily related to the age and vulnerability of the subjects. A clinical study on COVID-19 shows that antidepressants reverse the age-related vulnerability of patients (with SSRI, 73). In this study, the antidepressant group was older ($p < 0.001$) compared to the control group, but the death rate was similar (18% versus 17%, respectively); the antidepressant treatment completely reversed the effects of aging on COVID-19 infection. To test the age effect in host-resistance studies, it is essential to compare responses in old and young subjects. We expect a larger increase in survival with antidepressants in the aged group compared to the young group. Moreover, studies focusing on the elderly population could illuminate the potential benefits of antidepressants in enhancing host resistance in this vulnerable demographic group.

Some negative results, such as the lack of effect of amitriptyline (74) on wound healing, contrast with the efficacy of fluoxetine (64) and St. John's wort (65) in improving wound healing topically. The lack of efficacy with amitriptyline could result from studying young animals with optimal host resistance. We expect minimal benefits from antidepressants in young, healthy, non-stressed animals since their host resistance is already at its peak. Similarly, young, healthy individuals show minimal effects from antidepressants on mood. Older and stressed subjects will benefit more from the mood and trophic effects of antidepressants than young ones.

Antidepressants could be prescribed as add-on therapy with significant effects to reinforce host resistance during vaccination, infections, autoimmune conflicts, traumatic lesions, and aging. The effect of antidepressants on cell reproduction should be explored in infertility. In line with their trophic effects, antidepressants are suspected to promote graft rejection and cancer progression.

Clinicians should keep in mind that antidepressants

increase host resistance and reduce the lesions and pain due to an infection. The “pain” signal is reduced in every patient taking antidepressants. We have a clinical observation in which an older, depressed patient, treated with a high dosage of antidepressant, did not feel pain during a bacteriologically proven acute cystitis.

Understanding that antidepressants reverse the negative age-related effects on host resistance during stress, infections, and psychic and somatic trauma translates into an increase in cell, animal, and human survival with antidepressants.

Pharmacological pathways: Antidepressants Increase Host Resistance

The serendipitous discovery of the mood effects of antidepressants originated from their use as antibiotics. Monoamine Oxidase Inhibitors (MAOIs) were first used to treat tuberculosis, where antidepressant effects on mood were observed in sanatoriums. Despite the cross-talk between neurons and immune cells, with both systems presenting the same type of receptors on the cell membranes, we do not yet understand the circuitry that links the antidepressant molecule to the effects on mood and immunity. However, we have two pathways to explain the increase in host resistance.

Classical Mechanism of Action of the Antidepressant Effect

The monoamine theory, supported by the pharmaceutical industry, proposes that the augmentation of serotonin and/or noradrenaline neurotransmission is essential to the antidepressant effect. Antidepressants act on different neuronal and immune receptors (e.g., noradrenaline, serotonin, dopamine) to produce an effect through millions of unknown interactions between neurons. The underlying belief is that a pathway exists that should be activated to enhance mood and neurogenesis. Many pathways have been investigated that explain the side effects of antidepressants but not the mood/immunity effect.

We previously followed the neurotransmission theory and showed that all antidepressants increase dopamine in the frontal cortex of rats (with chemical antidepressants, electroconvulsive therapy, repetitive transcranial magnetic stimulation, sleep deprivation, 75), irrespective of their initial monoamine interactions on neuronal receptors. We also showed that a pure, selective D1 agonist (A77639) was sufficient by itself to induce an antidepressant-like effect in

the forced swim test (76). Our results propose that the D1 receptor agonism is sufficient to induce an antidepressant effect in an animal model of depression. This D1 agonist was shown to induce a powerful acidification of lysosomes and can functionally inhibit the ASM enzyme and reduce ceramides. (77) This leads us to the second pathway to explain host resistance with antidepressants.

The ASM / Ceramide Theory

The ASM / Ceramide theory suggests that some antidepressants functionally inhibit the enzyme ASM, causing a reduction in ceramide production over time. Research from Gulbins' group shows that a lipid-based pathway is involved in the pathology of depression. This pathway is activated by psychosocial stress, oxidative stress, and inflammation. Overload from the ASM/ceramide pathway under stress may account for depression, with its associated behavior and inflammation, since the accumulation of ceramides promotes inflammation and oxidative stress (78).

Ceramides and Depression

One recent study provides evidence for a novel concept in the pathogenesis of MDD and suggests potential new treatments (79). In this concept, MDD is initiated by a peripheral ceramide increase in response to stress and evolves to manifest itself in the brain. MDD affects the whole body, not just the brain. The study shows that stress generates ceramides, that ceramides are markers of depression, that ceramides induce depression, and that antidepressant therapeutics reverse depression and reduce ceramide levels.

Stress is induced by (i) chronic unpredictable environmental stressors and (ii) glucocorticoid administration in the water supply. The study demonstrates that ceramides are increased during depression. Patients suffering from moderate and severe major depression (Hamilton depression rating score ranging from 23 to 27 points for moderate and from 28 to 37 points for severe) show a marked increase ($p < 0.001$) in ceramide concentrations in the plasma compared to healthy individuals. A second, independent set of older MDD patients (average age 70 years) and controls (average age 68 years) confirmed the finding of an increase in ceramides in the MDD group ($p < 0.05$) compared to healthy controls (79).

Several other studies indicate that ceramide levels are increased in the blood plasma of patients with MDD (80-84) and that ceramides play a role in the pathogenesis of

depression. The authors demonstrate, in three different ways, that depression, along with its changes in neurogenesis and behaviors, is induced by ceramide administration (1) by injecting ceramide into rats and observing depression-like behavior ($p < 0.001$) (2) by injecting blood plasma from stressed mice into non-stressed, healthy mice and observing depression-like behaviors ($p < 0.001$) in the recipients, (3) by injecting plasma from stressed mice in which ceramides are inhibited, either by antibodies or ceramidase, and observing the lack of depression-like symptoms in the recipients.

The ASM/Ceramides pathway

Within cells, the ASM enzyme catalyzes the degradation of sphingomyelin into phosphorylcholine and ceramide. Ceramide accumulation increases oxidative stress, promotes the release of proinflammatory cytokines, and blocks hippocampal neurogenesis (85). Gulbins et al. (86), show that antidepressants (amitriptyline and fluoxetine) reduce ceramide levels in the hippocampus of stressed mice and increase neurogenesis. Their hypothesis is that conventional lysosomes can fuse with the plasma membrane (in response to elevations in intracellular Ca^{2+}), releasing their ASM content extracellularly (87). Antidepressants inhibit the ASM enzyme, likely on the cell surface of all cells and possibly in the cell's lysosomes to reduce the production of ceramides. Ceramide molecules may alter membrane biophysics. Their self-association within the cell membrane forms larger ceramide-enriched platforms, clustering receptors such as CD95 and FAS receptor. Activation of the FAS receptor leads to cellular death through a signaling cascade involving caspases, acidic sphingomyelinase, ceramide, and JNK/p38-K (69). Ongoing research explores how ceramides interact with cell membranes, receptors and neuro-transmission. (88)

The ASM/Ceramide theory proposes that antidepressants reduce ceramide accumulation to produce mood and trophic effects, ultimately contributing at the cellular level, to membrane stabilization and cell survival. This mechanism could explain the protective action of antidepressants in cell cultures and open wounds.

Ceramides and Antidepressants

Reducing ceramides, through various methods, reverses depression:

- Neutralizing or consuming ceramides (with antibodies

or ceramidases) restores normal functions in mice with MDD-like symptoms within 24 hours (79).

- Functional inhibition of the ASM enzyme by FIASMA antidepressants reverses clinical depression. By definition, FIASMA antidepressants exhibit residual activity $< 50\%$ on the ASM enzyme. The nine antidepressants tested by Beckmann et al. (70) and measured by Kornhuber et al. (19 antidepressants, 89) are all FIASMA. The residual ASM activity after 1/2-hour incubation is for amitriptyline: 11%, imipramine: 32%, clomipramine: 21%, desipramine: 15%, doxepin: 46%, lofepramine: 19%, nortriptyline: 13%, protriptyline: 12%, trimipramine: 13%. However, some antidepressants tested by Kornhuber (89) are not FIASMA, presenting $> 50\%$ residual activity of the ASM enzyme after incubation: citalopram: 79%, venlafaxine: 95%, and even less ASM inhibition than control cells: bupropion 117%, mirtazapine 100.2%, reboxetine 105%, mianserine 111%.

These studies demonstrate that not all antidepressants reduce ceramides. While the ASM/ceramide theory is incomplete, it explains some cellular and trophic effects of antidepressants on cell's membranes, and synapses. However, it does not explain the effects of non-FIASMA antidepressants (e.g., citalopram, venlafaxine, mirtazapine, mianserine, reboxetine, bupropion), in their ability to increase host resistance (e.g., reduced risk of hospitalization and progression to severe COVID-19 with venlafaxine and mirtazapine (8), with citalopram (15); reduced scarring in burns (with citalopram, 44), increased stem cell proliferation (with citalopram, 56), and attenuation of liver injury in mice (with mirtazapine, 39).

In our understanding, the monoamine theory and the lipid-based pathway theory should be combined. We propose that antidepressant activity results from either dopamine D1 agonism and/or serotonin increase, with or without the ASM lipid-based pathway.

CONCLUSION

Antidepressants reduce the perception of danger in the host (mood effect) and promote a trophic state in cells characterized by anti-inflammatory (immune system), cytoprotective, survival (cell and organism), and reproductive (stem cell) effects. These effects are partly explained by the ASM/ceramide pathway and partly by the monoamine theory of antidepressants. Together, they partly elucidate the observed increase in host resistance associated with all antidepressants.

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