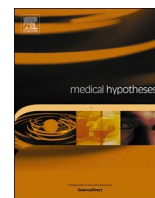




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Antihistamine and cationic amphiphilic drugs, old molecules as new tools against the COVID-19?

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A B S T R A C T

Several studies have reported that certain psychoactive drugs could have a protective effect against SARS-CoV-2. Herein, we propose that antihistamines (anti-H1) and cationic amphiphilic drugs (CAD), specifically, have the capacity to disrupt virus entry and replication. In addition, several of these molecules have limited side effects and as such could be promising prophylactic candidates against SARS-CoV-2 infection.

Introduction

The SARS-CoV-2 pandemic remains a challenge insofar as preventive and/or curative pharmacotherapeutic strategies have not been clearly identified yet. Among possible options, psychotropic drugs have been considered as possible prevention strategies. Indeed, given the numerous factors which might increase the risk of having a severe COVID in patients with psychiatric disorders, it is surprising that the initial prevalence of COVID, during the first wave and based on the first-published reports, was apparently similar or only slightly higher in patients with mental illness compared to the general population [1,2]. As some authors have recently suggested, this could be indicative of a prophylactic effect against SARS-CoV-2 shared by psychoactive agents commonly used to treat psychiatric patients [3,4]. Such a theory is supported by the characterization of antiviral effects in general and against coronaviruses in particular described for many old psychotropics [5,6].

Pharmacochemical based hypothesis

There is some literature about the efficacy of different pharmacotherapeutic classes on coronaviruses [6] which has been recently reviewed [3,4]. This has allowed to specify the drugs which could have antiviral activity, and, more specifically, possible anti-SARS-CoV-2 effects [3,4]. Based on the data provided by Dyal et al. [6] the class effect shared by phenothiazines (chlorpromazine, fluphenazine, promethazine, thiethylperazine, triflupromazine) could be extrapolated to other substances, such as cyamemazine and alimemazine/trimeprazine, which are commonly prescribed in France, but also levomepromazine or periciazine [3,4].

The 11 psychotropic drugs identified as potentially effective against coronaviruses by Dyal et al. [6] are antihistamines (anti-H1) and cationic amphiphilic drugs (CAD). The latter can cause intracellular trafficking disturbances, hence disrupting viral entry and replication [3,4]. From this standpoint, cationic amphiphilic drugs (CAD) could represent a preventive treatment against SARS-CoV-2. Cationic and

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Table 1

Substances with antihistamine and cationic amphiphilic characteristics, with potential (or confirmed) anti-SARS-CoV-2 activity [2,3]

| Psychotropics with antihistamine and cationic amphiphilic properties and potential anti-SARS-CoV-2 activity (FIASMAS +/-) | Preliminary data confirming anti-SARS-CoV-2 activity |
|---|--|
| Alimemazine/trimeprazine (- ¹) | [13] |
| Amitriptyline (+) | [8] |
| Astemizole (+) | |
| Benz(a)tropine (+) | [18] |
| Cetirizine (-) | |
| Chlorphenoxamine (-) | |
| Chlorpromazine (+) | [16,18,19] |
| Citalopram* (-) | |
| Clomipramine (+) | [19] |
| Clozapine (-) | † |
| Cyamemazine (- ¹) | |
| Escitalopram* (-) | [8] |
| Flupent(h)ixol (+) | [13] |
| Fluphenazine (+) | [19] |
| Fluspirilene*(- ²) | [19] |
| Hydroxyzine (+) | [17] |
| Levomepromazine/methotrimeprazine (- ¹) | |
| Mequitazine (- ¹) | |
| Metopimazine (- ¹) | |
| Penfluridol* (+) | |
| Pimozide* (+) | [21] |
| Pipamperone*(-) | |
| Pipotiazine (- ¹) | |
| Promethazine (+) | [19] |
| Pericy(y)azine/propericiazine (- ¹) | |
| Quetiapine (-) | |
| Tiethylperazine (- ¹) | [19] |
| Tiotixene (- ¹) | |
| Triflupromazine (+) | |
| Zuclopenthixol (- ¹) | |

* Very weak to weak antihistamine effects.

† Very likely that all clinically used phenothiazines (and closely-related compounds) belong to the FIASMAS, but not tested all experimentally.

fluspirilene is a diphenylbutylpiperidines related to pimozide, penfluridol and loperamide with FIASMA profile; not tested experimentally.

† Conflicting data in Govind et al.[27].

amphiphilic represent key physicochemical characteristics of a newly proposed classification of drugs related to their ability of acid sphingomyelinase (ASM) inhibition and called Functional Inhibitors of Acid Sphingomyelinase (FIASMAS) [7]. This property could also be linked to the endolysosomal anti-SARS-CoV-2 activity and of the 11 drugs described above, 7 are indeed confirmed FIASMAS [6,8,9].

Antihistamine properties are present in all the substances mentioned above, as well as in conventional antihistamines (astemizole, chlorphenoxamine), phenothiazines or structurally derived antipsychotics (thiothixene, fluspirilene), tricyclic antidepressants (clomipramine), and the anticholinergic (benztropine) [6]. Many antihistamine drugs are also CAD and as such could act on virus entry while, also exerting a negative regulation on IL-6 release from human lung macrophages which are secreted in great amounts during the cytokine-storm of COVID-19 [10,11]. The most recent data indicate that antihistamines (anti-H₁) medications in general and particularly phenothiazines and derivatives could be a useful strategy against SARS-CoV-2 at multiple stages, from prophylaxis to preventing complications of the infection itself [12–21]. Moreover, in a large sample of 219,000 electronic health records, 3 antihistamine medications (azelastine, diphenhydramine and hydroxyzine) were associated with reduced incidence of SARS-CoV-2 in subjects over the age of 61 [17].

Two overlapping lists of psychoactive agents with potential prophylactic effects against SARS-CoV-2 have been recently proposed in the literature based on pharmaco-epidemiological and pharmacochemical/chemoinformatic data. Both include mostly substances with antihistamine and cationic amphiphilic characteristics [3,4] (see Table 1).

It should be noted that this hypothesis was formulated based on the

initial data regarding the evolution of the pandemic in psychiatry [1,2,22]. Some recent results, however, suggest that suffering from a psychiatric disorder could increase the risk of being affected by COVID-19 [23] of developing a severe form of it [1] or even of dying as a result of it [24] while psychotropic drugs may increase COVID-19 mortality in elderly patients [25]. These data encouraged us to make assumptions about what could have constituted a possible initial prophylactic factor in psychiatry settings. Like the conflicting data around tobacco and nicotine [26] it is necessary to assess whether the increased risk of aggravation in mental health patients once hospitalized for COVID-19 could come from the possible reduction or cessation of all or part of psychotropic medications having a potential effect against SARS-CoV-2.

Perspective

Hence, we propose that molecules with antihistamine H₁ and cationic amphiphilic properties (single compound or combination) could have a protective effect against SARS-CoV-2 infection in patients with mental health disorders. Among these, the best-tolerated drugs with limited side effects could become promising prophylactic candidates to reduce the risk of SARS-CoV-2 infection in the general population. The benefice-risk assessment of such medications after hospitalization for COVID-19 in patients could also be evaluated.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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