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Dysregulation of G protein-coupled receptors of the autonomic nervous system, adrenergic and muscarinic acetylcholine receptors, in patients with autoimmune dysautonomic-related disorders

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G protein-coupled receptors (GPCRs) of the autonomic nervous system such as adrenergic and muscarinic acetylcholine receptors are located both in the peripheral and central nervous system. These receptors are expressed in various cell types including immune cells, cardiac and airway smooth muscle cells, salivary gland cells etc., and play a significant role in a diverse physiological processes in the human body such as vasoconstriction of blood vessels (of the skin, gut, kidney and brain), contraction of smooth muscles, heart rate, salivary secretion, cognition, regulation of movement of gastrointestinal tract etc. (Brodde et al., 2001; Kanagy, 2005; Strosberg, 1995; Taylor, 2007; Saternos et al., 2018). Evidence has been accumulated arguing for a role of autoantibodies against adrenergic and acetylcholine muscarinic receptors (and gene defects in these receptors) in the development of autoimmune diseases, both in experimental animal models (Huang et al., 2018; Liu et al., 2018) and in human patients ((Eng et al., 1992; Jazdzewski et al., 2007; Malysheva et al., 2008; Park et al., 2011; Smith et al., 2005; Xu et al., 2000)). For example, β2 adrenergic receptor (β2 AdR) signaling was reported to be involved in the pathogenesis of rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, myasthenia gravis etc. (Wu et al., 2018), while autoantibodies against muscarinic 3 acetylcholine receptor (M3 mAChR) has been found to be involved in the progression of Sjogren's syndrome and corresponding mouse models ((Yu et al., 2018a)). Recently, the appearance of these antibodies have been described to be dysregulated in various enigmatic and suspected immune/autoimmune-related disorders such as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) (Loebel et al., 2016; Scheibenbogen et al., 2018), post HPV vaccination syndrome, postural orthostatic tachycardia syndrome (POTS) (Li et al., 2014; Fedorowski et al., 2017; Yu et al., 2018b), complex regional pain syndrome ((Dubuis et al., 2014), (Kohr et al., 2011)) etc. For example, Loebel et al. found elevated antibodies against β2 AdR and M3/M4 mAChR in a subset of patients with ME/CFS. Importantly, a reduction in β2 AdR antibody levels was found in ME/CFS patients responding to ritixumab treatment ((Loebel et al., 2016)). Furthermore, in a proof of concept, pilot study, Scheibenbogen et al. observed that immunoadsorption is effective to remove β2 AdR autoantibodies and can induce a clinical improvement in post-infectious ME/CFS (Scheibenbogen et al., 2018). There is increasing evidence for the role of adrenergic and muscarinic receptors in immune

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function. For example, in monocytes, β2 AdR stimulation inhibits LPS-induced TNFα (Agac et al., 2018; Guirao et al., 1997). IL-10 release in monocytes is enhanced *via* β2 AdR stimulation ((Agac et al., 2018)). Disruption of physiological functions of M3R on T lymphocytes (which are known to express type 1–5 muscarinic receptors) is another possible cause for primary Sjogren's syndrome-induced leukopenia (Sato et al., 1999; Namkoong et al., 2017). In the current issue of Brain, Behavioral and Immunity journal, Hartwig et al. studied the functional effect of serum-derived IgG antibodies from ME/CFS patient as compared to healthy control samples, on β2 adrenergic receptor signaling and immune function. Using β2 AdR transfected reporter cell lines, the research group found that IgG from healthy control has an agonistic β2 AdR effect resulting in induction of β2 AdR signaling. Furthermore, they found that IgG from a healthy controls, similar to isoprenaline, a non-selective β adrenoreceptor agonist, reduced TNFα production and increased IL-10 production in human monocytes, and enhanced T cell proliferation. However, IgG from ME/CFS patients with elevated β2 AdR antibodies had no significant effects neither on β2 AdR signaling nor on immune cell function. These important finding clearly shows that IgG antibodies physiologically stimulates the β2 AdR and that this function is attenuated in ME/CFS patients which might explain many symptoms such as immune dysfunction-related manifestations and dysautonomia in these patients. Exploration of the functional activities of patients-derived antigen-specific affinity-purified antibodies (rather than total IgG purification) against adrenergic/muscarinic receptors using functional assays is of interest and needed in future research.

We need to keep in mind that functional autoantibodies targeting GPCRs such as adrenergic and muscarinic receptors are able to activate (agonist autoantibodies) or inhibit (antagonist autoantibodies) intracellular signalling pathways that are normally triggered by endogenous ligands (epinephrine, acetylcholine etc.) to mediate a particular cellular function ((Cabral-Marques and Riemekasten, 2017)). Moreover, the appearance of these autoantibodies might be found also in healthy subjects, thus, the confirmation of that functional activity of these patients-derived antibodies as compared to healthy volunteers, is of an importance, as already suggested by the study of Hartwig et al.

Li et al., recently demonstrated for the first time the *in vivo* role of adrenergic autoantibodies in the pathophysiology of POTS. In that study, co-immunization of rabbits with peptides of α1 and β1-adrenergic receptors, lead to the production of functional α1AR and β1AR-autoantibodies, and to changes in cardiovascular responses to catecholamines, contributing to the POTS-like phenotypes. Moreover, the effect of these adrenergic autoantibodies was found to be reversed using selective decoy peptide inhibitors ((Li et al., 2019)). *In vivo* passive transfer of the patients-derived autoantibodies themselves into animals, following examination of relevant pathologies (immune dysfunction, cognitive impairment, neurological dysfunction etc.) is extremely important for the exploration of potential direct role of these antibodies in the pathogenesis of suspected immune/autoimmune-related enigmatic and unexplained disorders ((Ryabkova et al., 2019)). Moreover, as adrenergic and muscarinic acetylcholine receptors are expressed on various cell types and locations in our body, the specific binding target sites of these patient-derived autoantibodies can be explored using immunohistochemistry/immunofluorescence staining of these antibodies in the relevant tissues of interest, following intravenous or local injection of these antibodies into animals.

We recently found the appearance of various circulating autoantibodies against muscarinic and adrenergic receptors in women with silicone breast implants (SBIs), suffering from diverse clinical manifestation, among them chronic severe fatigue, sleep disturbance, widespread pain, memory loss, dry mouth, depression, hearing abnormalities etc. (personal communication). Notably, in a large population-based study, our group have demonstrated recently, an association between SBIs and the presence of autoimmune/rheumatic disorders ((Watad et al., 2018)). Silicone is a non-self, foreign material to our body and has been found to act as an adjuvant in our body (in contrast to what was thought for many years) and to chronically stimulate the immune system leading to the activation of the acquired immune system ((Watad et al., 2019)). This chronic stimulus may lead to autoimmune reaction accompanied by the newly production of autoantibodies or augmentation of natural antibodies production against autonomic nervous system such as muscarinic and adrenergic receptors, which we believe, may explain, at least in part, some of the subjective clinical manifestations reported by SBIs patients.

Overall, we suggest that detecting abnormal circulating autoantibodies level against GPCRs such as adrenergic and muscarinic receptors, along with examination of potential dysfunctional activities of these antibodies (both *in vitro* and *in vivo*) to confirm their dysregulation of physiological processes in our body, might serves as a revolutionized objective tool and as a biomarker, for the prognosis and potential future therapies of a group of suspected autoimmune dysautonomic-related disorders such as ME/CFS, fibromylagia, silicone breast implants etc.

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