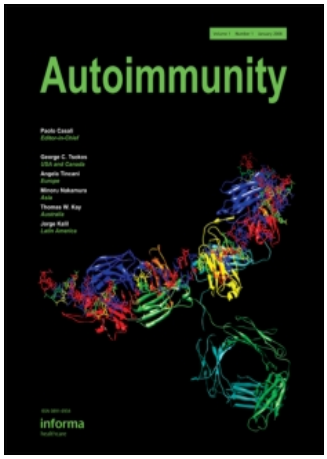

Autoimmunity
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713453864

Streptococcal mimicry and antibody-mediated cell signaling in the pathogenesis of Sydenham's chorea

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Online Publication Date: 01 February 2006
To cite this Article: Kirvan, Christine A., Swedo, Susan E., Kurahara, David and Cunningham, Madeleine W. (2006) 'Streptococcal mimicry and antibody-mediated cell signaling in the pathogenesis of Sydenham's chorea', Autoimmunity, 39:1, 21 - 29
To link to this article: DOI: 10.1080/08916930500484757
URL: http://dx.doi.org/10.1080/08916930500484757

Autoimmunity, February 2006; 39(1): 21–29

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Streptococcal mimicry and antibody-mediated cell signaling in the pathogenesis of Sydenham's chorea

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Abstract
Recent evidence suggests that the pathogenesis of Sydenham's chorea following group A streptococcal infection is due to antibodies which develop due to the infection and infiltrate the brain and basal ganglia. Antibodies present in acute chorea react with the surface of neuronal cells and signal the induction of calcium calmodulin dependent protein kinase II with elevation of tyrosine hydroxylase and subsequent dopamine release which may lead to the movement disorder. The antibodies present in disease recognize lysoganglioside and the group A streptococcal epitope, *N*-acetyl-glucosamine. Monoclonal antibodies (mAbs) from Sydenham's chorea demonstrated the mimicry between lysoganglioside and the group A streptococcal carbohydrate epitope. A group of antibodies present in pediatric autoimmune neuropsychiatric disorders (PANDAS) were similar but not identical to the antibodies observed in chorea.

Keywords: *Streptococci, autoimmunity, rheumatic fever, chorea*

Introduction

Group A streptococcus (*Streptococcus pyogenes*) is specifically associated with the development of post-infectious autoimmune responses in humans. The best studied of these responses is acute rheumatic fever (ARF), a delayed sequela of streptococcal pharyngitis, which produces significant morbidity and mortality in children worldwide. ARF represents a collection of inflammatory disorders in which immune activation by streptococcal antigens appears to initiate events resulting in inflammatory and autoimmune responses against the heart (carditis), joint (arthritis), skin (erythema marginatum and subcutaneous nodules) and/or brain (Sydenham's chorea) that produce the characteristic symptoms of ARF in susceptible individuals [1]. Since the mid-1980s there has been an unexplained resurgence in the number of reported ARF cases in the US and ARF continues unabated in developing nations [2,3]. While the last 50 years have seen striking advances elucidating the molecular mechanisms of pathogenesis in rheumatic carditis, information has only recently been forthcoming concerning the postinfectious mechanisms of streptococcal–induced central nervous system (CNS) dysfunction [4–9].

Sydenham's chorea is the neurologic manifestation of ARF. This confounding disorder is characterized by involuntary movements and neuropsychiatric disturbances, including obsessive-compulsive symptoms, hypersensitivity, and emotional lability (for review [10]). Sydenham's chorea can develop in 10–30% of ARF cases and may be the only manifestation of ARF presenting as late as 6 months after the initiating streptococcal pharyngitis [11,12]. Diagnosis of Sydenham's chorea and ARF are dependent on

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ISSN 0891-6934 print/ISSN 1607-842X online © 2006 Taylor & Francis
DOI: 10.1080/08916930500484757

correlation of symptoms with elevated anti-streptolysin O (ASO) or DNase B titers, however, the delayed onset of Sydenham's chorea can make diagnosis difficult.

While several infectious agents have been implicated in the induction or exacerbation of postinfectious autoimmunity, group A streptococci are well established as inducers of cross-reactive antibodies through molecular mimicry with host antigens [13–15]. Such cross-reactive antibodies can be classified according to their molecular specificity: (1) polyreactive antibodies that recognize similar chemical or conformation structures on distinct streptococcal and host antigens [16] and (2) multireactive antibodies that react with dissimilar chemical or conformational structure such as protein and carbohydrate [7,17–19]. Considerable evidence has shown that crossreactive immune responses against group A streptococci and host antigens leads to rheumatic carditis [6,8], and it is likely that Sydenham's chorea is mediated by similar events through production of a cross-reactive humoral response directed against neuronal determinants in the brain [14,20]. The basal ganglia is implicated as one of the primary cortical targets of poststreptococcal immune responses by clinical observations and magnetic resonance imaging (MRI) data suggesting that basal ganglia insults are by antibodies which contribute to pathology in Sydenham's chorea [21,22]. Early characterizations of Sydenham's chorea autoantibody responses showed reactivity with neuronal antigens in human basal ganglia cross-sections with anti-neuronal antibody titers associated with both severity and duration of choreic episodes [23,24]. Recent studies confirm the presence of antibodies against basal ganglia in Sydenham's chorea [25–28].

Streptococcal surface antigens are implicated in the generation of cross-reactive immune responses in ARF. In the early 1980s, monoclonal antibody (mAb) studies identified two cross-reactive antigens for ARF that are unique to group A streptococci [13,14,17,29]. The first is the streptococcal M protein, an antiphagocytic virulence factor that shares sequence and structural homology with many mammalian proteins including human cardiac myosin (HCM), tropomyosin, actin, keratin and laminin [16,29–31]. The second cross-reactive antigen identified was *N*-acetyl-β-D-glucosamine (GlcNAc), the immunodominant epitope of the group A carbohydrate (GAC) [18,19,32]. GlcNAc residues are bound to a rhamnose polymer backbone by β-1,3 linkages with terminal GlcNAc moieties recognized by GAC-specific antibodies [33–36]. Both the M protein and GAC have been implicated in the generation of anti-heart antibodies that contribute to rheumatic carditis and it is probable that these antigens induce cross-reactive immune responses directed against neuronal antigens in the brain [7,37].

Husby et al. were the first to characterize CNS reactivity of Sydenham's chorea antibodies [24]. Recognition of cytoplasmic antigens in fixed human caudate and subthalamic nuclei cross-sections by Sydenham's chorea sera antibodies was absorbed with membranes of rheumatogenic streptococcal strain M type 6, indicating that bacterial cell wall components may evoke cross-reactive anti-neuronal antibodies. To elucidate the role of streptococcal antigens in Sydenham's chorea, Bronze and Dale demonstrated that immunization of experimental animals with M protein of rheumatogenic serotypes induced cross-reactive antibodies capable of recognizing multiple proteins from human brain [23]. Conserved epitopes contained in A and B repeat regions of the M protein could inhibit M protein antisera recognition of human brain antigens, however, the neuronal antigens were not identified. These pioneering studies were the first to clearly link streptococcal antigens to the development of a cross-reactive antibody response in Sydenham's chorea. Studies in our laboratory revealed that recognition of the extracellular digestion fragment of type 5 streptococcal M protein (pepM5) by Sydenham's chorea serum antibodies was associated with the symptomatic phase of the disorder. Acute Sydenham's chorea sera showed significantly greater reactivity to pepM5 than did matched patient convalescent sera, indicating that elevated levels of M protein-specific antibodies were present during illness and decreased with diminishing severity of symptoms (Figure 1). Although, the data suggest antibodies directed against the streptococcal M protein are associated with Sydenham's chorea, the exact role and cross-reactivity of anti-M protein antibodies requires further study. In the future, mAbs against the M protein and brain may be able to clarify this issue.

Determination of cross-reactive specificities between streptococcal and neuronal antigens is complicated by the polyclonal antibody response in Sydenham's chorea. Recently, mAbs derived from a Sydenham's chorea patient were employed to uncover the identity of cross-reactive antigens [38]. When tested against a panel of streptococcal and mammalian antigens, chorea mAbs demonstrated significant reactivity with only the GlcNAc epitope (Figure 2). Chorea mAbs showed no recognition of the M protein from rheumatogenic serotypes 5 and 6 and demonstrated minimal reactivity for cardiac antigens in direct contrast to human GlcNAc-specific mAbs from rheumatic carditis that were strongly cross-reactive with HCM and laminin [6]. Interestingly, the chorea mAbs showed no reactivity to keratin, which is a pronounced characteristic of human anti-GlcNAc antibodies against epitopes in the skin [18,19].

GlcNAc is capable of generating strong humoral responses during active streptococcal infection and in post-infectious sequela [39,40]. It has been suggested

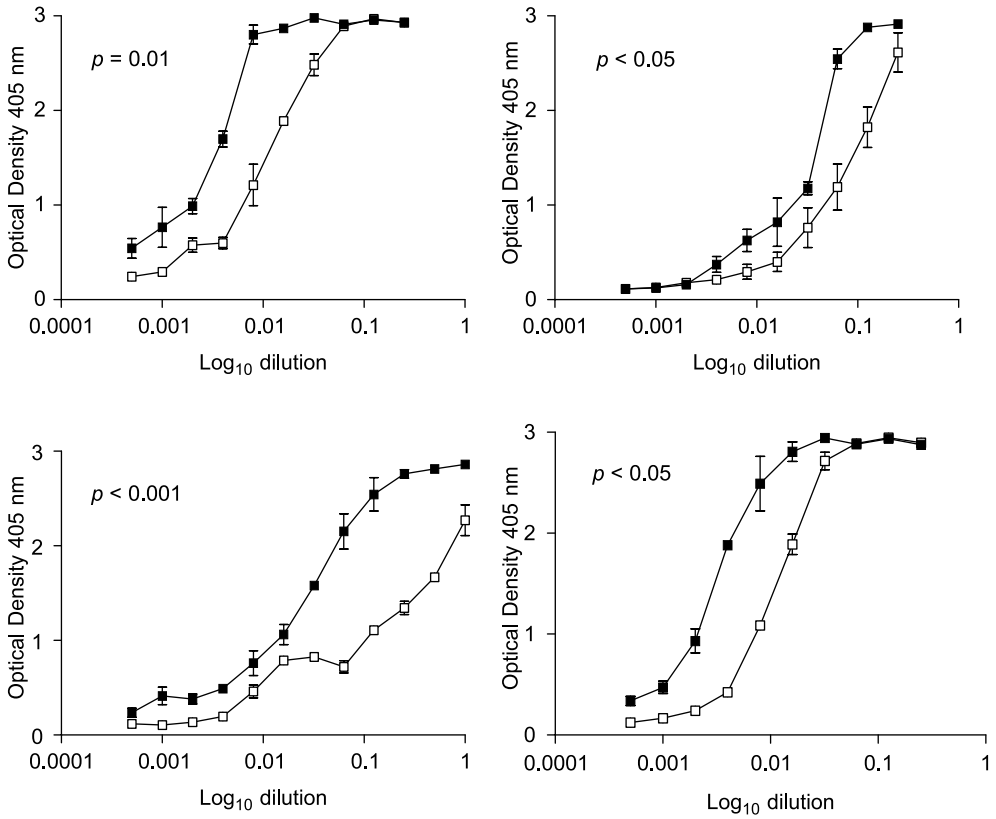

Figure 1. M protein-specific antibody in Sydenham's chorea. Serial dilutions of matched Sydenham's chorea acute (■) and convalescent (□) sera show significantly elevated levels of pep M5-specific IgG are associated with the symptomatic phase of illness in four separate Sydenham's chorea patients. Each graph represents matched acute and convalescent sera from an individual patient.

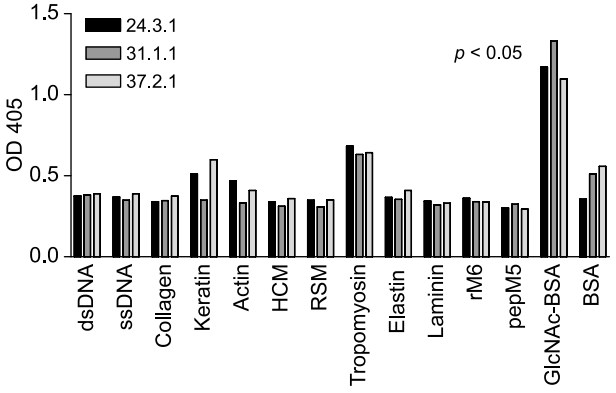

Figure 2. Reactivity of chorea mAbs with streptococcal and mammalian autoantigens. Chorea mAbs showed significant reactivity ($p < 0.05$) with the immunodominant carbohydrate epitope (GlcNAc) of group A streptococcus in comparison to other antigens tested by two-tailed t test. The chorea mAbs did not bind to either the fragment of streptococcal M protein (pepM5) or full length recombinant streptococcal M6 protein (rM6). Chorea mAb reactivity was significantly greater with the GAC than with dsDNA, collagen, actin, skeletal myosin, tropomyosin and laminin. Chorea mAbs also failed to recognize HCM, which is characteristic of mAbs produced from patients with rheumatic carditis, nor did chorea mAbs strongly react with keratin which characterizes GlcNAc-specific mAbs reactive with skin.

that terminal O-linked GlcNAc residues may be important in the induction of cross-reactive antibodies due to its structural similarity to many host glycoconjugates. Antibodies specific for the GAC were found capable of recognizing a variety of host tissues and studies with human and murine anti-GlcNAc mAbs demonstrate specific cross-reactivity with mammalian proteins [7,19,41]. Immunization of experimental animals with GlcNAc gives rise to T cell-dependent antibody responses to cytoskeletal proteins, particularly keratin and cardiac myosin [17,42]. ARF patients with valvular heart disease were shown to have persistently high levels of antibodies to the streptococcal carbohydrate [40]. Elevated levels of GAC-specific antibodies have been demonstrated in Sydenham's chorea patients [40,43]. Recently, we have observed that acute sera from patients with Sydenham's chorea showed significantly elevated titers to GlcNAc that decreased with the abatement of symptoms. These data indicate that antibodies directed against GlcNAc and the GAC may play an important role in mediating the clinical symptoms and immunopathogenesis of Sydenham's chorea.

Sydenham's chorea mAbs specific for GlcNAc were found to cross-react with mammalian gangliosides [38]. Gangliosides are a diverse family of glycolipids that show specific developmental and differential

expression within the brain and contribute to multiple functions mediated at the cell surface, including signal transduction [44,45]. Mimicry between gangliosides and the GlcNAc epitope has been classified as "dissimilar" as defined previously in studies of mimicry between GlcNAc and peptide structures [17–19]. Identification of cross-reactive antibodies, which recognize dissimilar epitopes is not limited to ARF. Investigation of cross-reactive antibody responses in the neuropyschiatric disorders of systemic lupus erythematosus (SLE) demonstrated that a DNA-specific mAb also recognized subunits of the *N*-methyl-D aspartate (NMDA) receptor in the hippocampus [46].

Competitive inhibition studies with GlcNAc revealed that Sydenham's chorea mAbs were strongly cross-reactive with lysoganglioside G_{M1}, a CNS ganglioside shown to influence neuronal signal transduction [38,44]. Increased levels of anti-lysoganglioside G_{M1} antibodies correlated with active chorea. Significantly higher anti-lysoganglioside G_{M1} antibody concentrations were also found in Sydenham's chorea acute sera but not in matched convalescent sera or sera from patients with acute ARF without Sydenham's chorea. Acute Sydenham's chorea cerebrospinal fluid (CSF) samples were found to have elevated levels of anti-lysoganglioside G_{M1} IgG in comparison to control CSF, indicating that lysoganglioside G_{M1}-specific antibodies were present in the CNS during active disease. Lysoganglioside G_{M1} was also found to block Sydenham's chorea mAb and acute sera binding to human caudate-putamen tissue indicating that it is potent and specific inhibitor of Sydenham's chorea antibody reactivity to human brain tissue.

Recognition of neuronal cell surface determinants by chorea mAbs and sera suggested that Sydenham's chorea antibody binding might alter neuronal cell function. Previous reports have suggested that anti-ganglioside antibodies affect the physiologic homeostasis of neuronal cells through alteration of signal transduction pathways in neuroblastoma cells [47,48]. Sydenham's chorea mAbs and sera were shown to trigger calcium/calmodulin-dependent protein (CaM) kinase II activation in the catecholamine-secreting neuroblastoma cell line SK-N-SH [38]. Antibody-induced CaM kinase II activation appeared to be due to specific antibody induction (Figure 3) and not due to a general influx of calcium ions as chorea antibodies did not significantly activate protein kinase C or cAMP-dependent protein kinase above control levels (data not shown). CaM kinase II is a multi-functional protein kinase with a broad spectrum of neuronal targets and was of particular interest due to its functions in the CNS that influence behavior and neurotransmitter synthesis and release [49–52]. Antibody-mediated CaM kinase II activation was induced by Sydenham's chorea acute, but not convalescent sera, suggesting that increased CaM kinase II activity is associated with the active disease state (Figure 3). Intrathecal antibody from Sydenham's chorea CSF directed significant levels of CaM kinase II activation demonstrating that alteration of signal transduction events was present in the CNS (Figure 3). Pathogenic antibodies in Sydenham's chorea may directly bind to gangliosides or indirectly cause aggregation of neuronal receptors by binding to gangliosides, which trigger a signal transduction cascade.

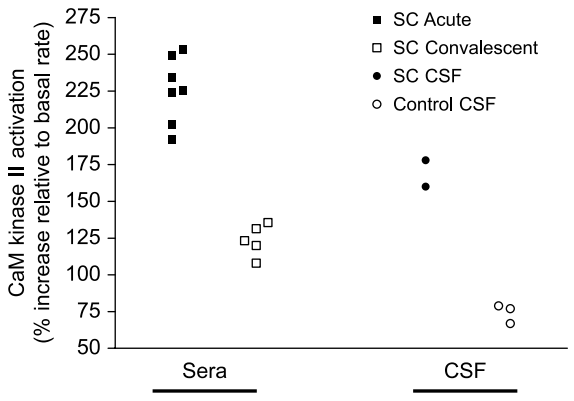

Figure 3. Induction of CaM kinase by Sydenham's chorea sera and CSF. Acute sera from Sydenham's chorea significantly ($p < 0.05$) activated CaM kinase II. Matched convalescent serum induced significantly lower levels of enzyme activity that found in acute sera The range for NHS induction of CaM kinase II was 98–116% of the basal rate. Sydenham's chorea CSF induced CaM kinase II while control CSF did not.

The ability of chorea antibodies to induce CaM kinase II activity directly correlated with avidity for lysoganglioside G_{M1}. Of the Sydenham's chorea mAbs tested, only chorea mAb 24.3.1, which demonstrated the highest avidity for lysoganglioside G_{M1}, was capable of mediating CaM kinase II activation. Antibody recognition of cell surface gangliosides other than lysoganglioside G_{M1} did not activate CaM kinase II suggesting that strong cell surface binding alone or binding of gangliosides in general does not induce CaM kinase II. Antibody from acute Sydenham's chorea sera and CSF were shown to have higher avidity and/or concentration in comparison to matched convalescent samples. Lower CaM kinase II activation was induced by sera from active ARF without Sydenham's chorea and acute streptococcal pharyngitis, which have significantly lower levels of anti-lysoganglioside G_{M1} antibodies indicating that a threshold concentration of specific antibody may be required for induction of cell signaling. The higher avidity of Sydenham's chorea mAb 24.3.1 for lysoganglioside G_{M1} and higher levels of anti-lysoganglioside G_{M1} antibody present in Sydenham's chorea acute sera and CSF suggests that anti-lysoganglioside G_{M1} antibody avidity, specificity, and/or concentration may trigger cell signaling events.

Anti-ganglioside antibodies have been reported to contribute to other neurologic disorders. Guillian-Barre syndrome is a post-infectious, antibody-mediated neurological disorder thought to be initiated through molecular mimicry between *Campylobacter jejuni* lipopolysaccharide and monosialoganlioside G_{M1} [53]. Cross-reactive antibodies direct complement-mediated cytotoxicity at the motor nerve terminal which may contribute to the loss of motor function associated with Guillian-Barre syndrome [54–56]. Localization of Sydenham's chorea sera antibodies to the neuronal cell membrane indicated the potential of antibody-induced, complement-mediated cytotoxicity. Acute Sydenham's chorea sera and CSF were assessed for cytotoxic potential by ^{51}Cr-release assay. Complement-dependent killing of human neuronal cell did not appear to be a major mechanism of pathogenesis (Table I). Additional studies revealed that Sydenham's chorea mAbs were also found to lack the ability to direct complement-mediated cytotoxicity. The non-destructive nature of Sydenham's chorea anti-GlcNAc mAbs is in contrast to anti-GlcNAc mAb derived from rheumatic carditis which was capable of directing complement mediated killing of endothelial cells, suggesting that there are different populations of anti-GlcNAc antibodies in ARF [7]. The inability of Sydenham's chorea antibodies to direct complement-mediated lysis supports the hypothesis that antibodies which change the physiology of the brain, rather than cytotoxic antibodies, contribute to the disorder. While MRI studies of Sydenham's chorea patients showed enlargement of the basal ganglia, evidence of physical damage, including lesions, to the brain has rarely been demonstrated [22,57]. The lack of Sydenham's chorea antibody cytotoxicity also complements plasma exchange studies which show rapid reversal in the clinical course of Sydenham's chorea patients with the removal of serum antibody [58].

It is unclear how antibodies mediate neurologic dysfunction in Sydenham's chorea. Clinical data suggests that antibodies in Sydenham's chorea, such as mAb 24.3.1, promote signal transduction that may lead to the release of excitatory neurotransmitters. It is of interest and importance in Sydenham's chorea that CaM kinase II activation has recently been associated with increased dopamine release in neuronal cell lines and brain slices [59]. Dopamine exocytosis can be mediated by CaM kinase II phosphorylation of synapsins, synaptic vesicle proteins that regulate neurotransmitter release [60–62]. In our studies, preliminary data shows that Sydenham's chorea mAb 24.3.1 elicited ^{3}H-dopamine release from SK-N-SH neuroblastoma cells in contrast to isotype control (Figure 4(a)). In addition, Sydenham's chorea acute sera was capable of evoking significant levels of ^{3}H-dopamine release in comparison to matched convalescent samples and pooled normal human sera (NHS) (Figure 4(b)). Tyrosine hydroxylase is the rate limiting enzyme in dopamine synthesis and tyrosine hydroxylase activity can be increased by CaM kinase II phosphorylation of the enzyme [63,64]. To determine if chorea mAbs were capable of stimulating increased tyrosine hydroxylase synthesis, Sydenham's chorea mAb 24.3.1 was passively transferred into rat brain and the level of tyrosine hydroxylase was determined by immunohistochemistry. Chorea mAb 24.3.1 induced higher levels of tyrosine hydroxylase in cerebral neurons than isotype control (Figure 4(c)). The increase in tyrosine hydroxylase level was seen only in neurons of the cerebrum and not of the cerebellum (Figure 4(c), inset). While neurons that showed an increase in tyrosine hydroxylase level have not been conclusively identified as part of the basal ganglia, the data suggest that Sydenham's chorea antibodies increase catecholamine synthesis *in vivo*. The ability of chorea antibodies to alter neurotransmitter synthesis and release may explain the efficacy of dopamine receptor blockers such as haloperidol in the treatment of Sydenham's chorea [65]. Our recent studies have led to the development of an antibody-mediated model of pathogenesis for Sydenham's chorea (Figure 5). Chorea antibody binding to the neuronal cell surface antigen triggers CaM kinase II activation that leads to an increase in the synthesis and exocytosis of dopamine through activation of tyrosine hydroxylase. Elevated levels of dopamine in the synapse may contribute to the movement and neuropyschiatric characteristics of Sydenham's chorea.

PANDAS

The last decade has witnessed a growing interest in neurologic disorders which share similar clinical manifestations with Sydenham's chorea. Increased attention has focused on a relatively new subgroup of childhood onset obsessive-compulsive disorder (OCD) and tic disorders known as Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS). The subgroup is distinct from other cases of childhood OCD and tic disorders in that the onset and exacerbation of neuropsychiatric symptoms is preceded by a Group A streptococcal infection [66,67]. Sydenham's chorea and PANDAS share similar neuropsychiatric symptoms and a common infectious etiology has been proposed for both disorders [68,69]. Anti-neuronal antibodies have also been demonstrated in PANDAS raising the possibility that development of clinical manifestations in Sydenham's chorea and PANDAS may be mediated through a similar antibody-directed mechanism of pathogenesis [70,71]. Recently, we have shown that PANDAS serum IgG reacted with the GlcNAc epitope of the streptococcal GAC and lysoganglioside G_{M1} as in Sydenham's chorea [72].

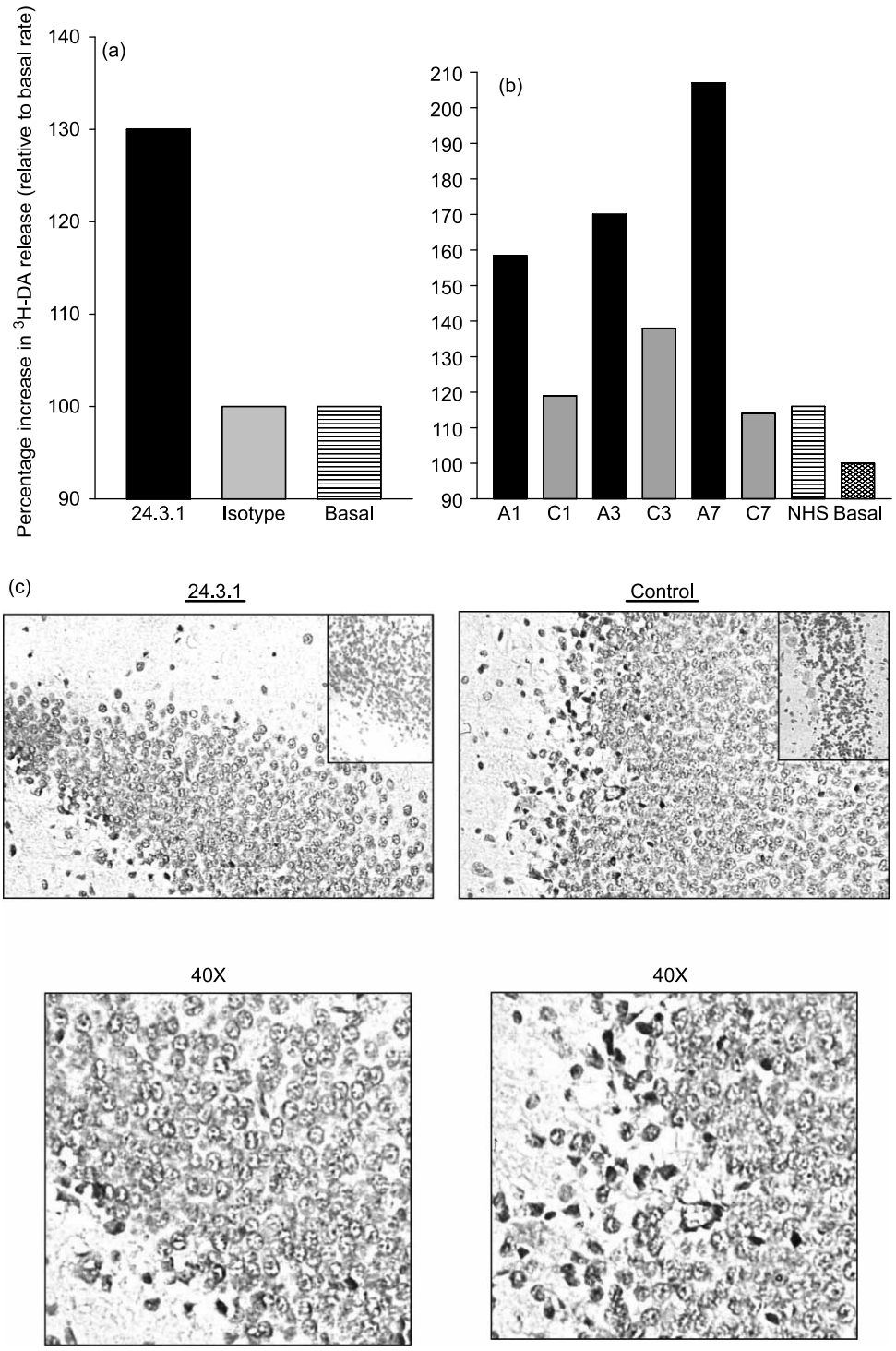

Figure 4. (a) Sydenham's chorea mAb 24.3.1 induced a higher percentage release of 3H-dopamine from SK-N-SH cells that isotype control. SK-N-SH cells were plated at 1 × 106 cells/well. For radioactive dopamine uptake, cells were incubated with 3H-dopamine for 90 min in modified Kreb's ringer buffer with 1 uM doperidone, 10 uM nomifensine, 100 nM nisoxetine, 100 nM fluoxetine, 0.1 mM ascorbic acid, 2 mM $CaCl_2$, 3 mM KCl and 0.2 mM $MgCl_2$ under standard tissue culture conditions. Cells were then thoroughly washed and antibody was added to the wells. After a 30 min incubation, supernatants were collected and 3H-dopamine was measured by scintillation counting. Values were expressed as percentage of 3H-dopamine basal release. Statistical analysis performed by two-tailed *t*-test. (b) Acute Sydenham's chorea acute sera induced significantly more 3H-dopamine release than matched convalescent sera or pooled NHS. (c) Sydenham's chorea mAb 24.3.1induced increased levels of tyorsine hydroxylase *in vivo.* Chorea mAb 24.3.1 or isotype control were passively transferred into intracerebroventricular cannulated Lewis rats (Hilltop Lab Animals, Inc.) every day for five consecutive days. Brains were removed and formalin fixed. Comparative levels of tyrosine hydroxylase were assessed by immunohistochemistry on whole brain cross-sections. The sections were probed with a tyrosine hydroxylase-specific antibody, developed with Fast red substrate, and counterstained with hematoxylin. mAb 24.3.1 induced higher levels of tyrosine hydroxylase than the isotype control. Elevated levels of tyrosine hydroxylase induced by chorea mAb 24.3.1 were seen in cortical neurons, but not in cerebellar neruons (inset).

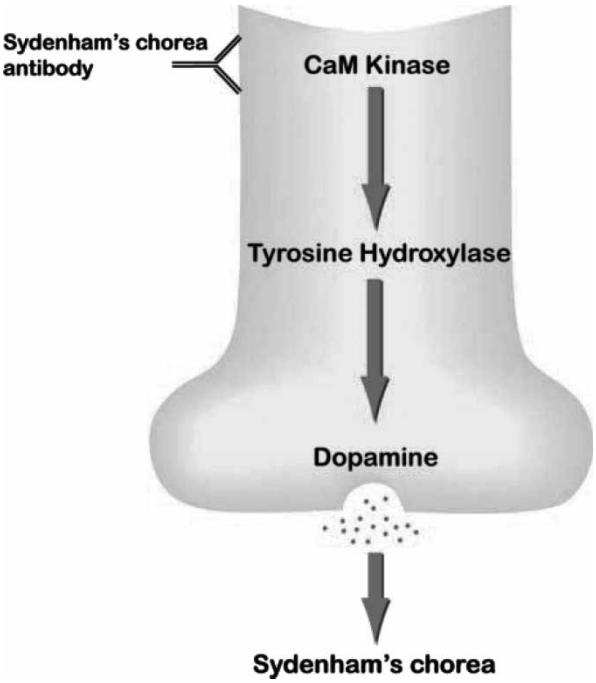

Figure 5. Proposed model of antibody-mediated pathogenesis in Sydenham's chorea. Sydenham's chorea antibodies bind to cell surface neuronal antigen triggering elevated levels of CaM kinase II activity. Increased CaM kinase II activity may induce an increase in the activity of tyrosine hydroxylase leading to enhanced dopamine release. Higher levels of dopamine in the synapse may contribute to the clinical symptoms associated with Sydenham's chorea.

PANDAS sera induced CaM kinase II activity in SK-N-SH human neuroblastoma cells similar to that seen in Sydenham's chorea with significant increases in CaM kinase II activity found for PANDAS sera during acute disease, but not in convalescent sera. Depletion of IgG from PANDAS serum abrogated CaM kinase II activation in comparison to non-depleted serum. PANDAS CSF was shown to increase neuronal cell signaling and demonstrated differential staining of human basal ganglia similar to Sydenham's chorea. Although group A streptococci induction of PANDAS has not been clarified, the new data suggest that antibody-mediated neuronal cell signaling may play an influential role in the immunopathogenesis of PANDAS.

Summary

Molecular mimicry between streptococcal antigens and neurological determinants in Sydenham's chorea is incompletely understood. Although there are only a limited number of studies on the mechanism of antibody pathogenesis in Sydenham's chorea, the cross-reactivity between the GAC and brain derived ganglioside appears to be important in the disease process. While studies have not definitively identified neuronal cell target antigen(s) in Sydenham's chorea, antibody-mediated signal transduction via CaM kinase II and subsequent disruption of neurotransmitter synthesis and release may be a potential mechanism in the immunopathogenesis of Sydenham's chorea and related disorders.

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