TRANSLATIONAL RESEARCH

S.07: **Translational insights into compulsivity** Forum **Sunday** 09:00-10:40

Neuroimmunological regulators of compulsivity

Tomorrow morning's symposium, 'Translational insights into compulsivity,' concludes with Giovanni Laviola (Istituto Superiore di Sanità, Rome, Italy) discussing his recent work on identifying the neuroimmunological regulators of compulsivity. Dr Laviola and colleagues have published a series of works over the past decade exploring the consequences of immune disruption in animal models, and he related these findings to compulsive behaviours during an interview with *ECNP Daily News*.

Dr Laviola began by describing the emergence of his present ideas: "Everything started almost 10 years ago, with the input of a Russian colleague, Dr Oleg Granstrem [Pavlov's State Medical University, St. Petersburg, Russia], who was working at Emory University [Atlanta, USA] with Professor Svetlana Dambinova. They were interested in the detection of autoantibodies (aAbs) against various glutamate receptors as a diagnostic tool for ischemic stroke consequences and prevention."

While doing so, Dr Granstrem also designed small fragments corresponding to the sequence of the dopamine transporter (DAT) protein, based on the most likely extracellular location of an epitope supposedly bound by aAbs.

With these DAT-derived fragments in their hands, Dr Laviola (along with colleague Walter Adriani of Rome's Istituto Superiore di Sanità) conducted a repeated immunisation study in mice.[1] "As expected, the immunised animals were found to actively generate DAT-directed aAbs," recalled Dr Laviola. "Notably, their immune activation was accompanied by profound changes in behaviour – the flexibility to shift a choice in operant paradigm settings, as well as slight hyperactivity and altered dopaminergic parameters in the striatum.

"It was then easy to speculate that the presence in plasma of DAT-directed aAbs could in some way be associated with their targeting the brain and thus affecting changes in procedural memory, if not even in the formation and expression of behavioural habits, in human subjects as well."

Just how far these mechanisms can be ascribed to the precipitation of analogous behaviours in human psychiatric illness, relative to other factors, remains a knotty question; but the field is young, with clues abundant in the literature: "Some psychiatric conditions linked to some autoimmune forms of encephalitis have been ascribed to, for example, NMDA-aAbs and/or AMPA-aAbs. But nothing is known yet for DAT-aAbs.

"For ADHD-related symptoms, the only study available so far is our own, in which we investigated affected children with or without methylphenidate administration therapy. It should also be noted that we reported the behavioural landmarks and plasma levels of DAT-aAbs interacting with the presence of polymorphisms in the DAT protein (the variable number tandem repeat (VNTR) alleles). This means that autoimmune mechanisms in this case are not likely to act alone – rather, they interact with genetic factors."[2]

The basis of behaviours characteristic of ADHD – alongside compulsive behaviours in substance abuse, gambling disorder, hypersexuality, OCD, Tourette's syndrome, and others – is a leading research theme. Moreover, explained Dr Laviola, the possibility that aAbs might tap directly into neural striatal circuits is intriguing.

Drs Laviola and Adriani's 2012 paper outlines some of the mechanisms by which immune insults on the brain might be mediated[1]. Considering the notion that the immune system is continuously involved in the formation of autoantibodies, Dr Laviola described how this might in some select circumstances lead to psychopathology: "Normally, the cell clone producing an aAb will be terminated, because the target epitope is recognised as 'self'. But – as is the case in multiple sclerosis, wherein a cell clone starts to produce aAbs against myelin – is it not possible that another cell clone could produce aAbs fighting against dopamine terminals in the striatum?

"In the case of the DAT 10/10 polymorphism, it is likely that there is a genetically-driven overproduction of DAT. The elevation in DAT-aAbs may well be considered as an adaptive process aimed to counteract the excessive DAT levels. If this is true, autoimmunity should be regarded not as a pathology, but instead as a 'normal' homeostatic process. The pathology may stem from a disruption of this immune control over genetic expression of a protein."

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Dr Laviola believes that aAbs could be harnessed as biomarkers of immune processes regulating neurotransmission proteins such as DAT, and perhaps even dopamine receptors, with non-invasive peripheral measures providing a window on goings on within the brain. He also noted that brain DAT function is highly relevant with respect to vulnerability to compulsive syndromes, as well as to some addictive behaviours, to ADHD, and to risk-taking and sensation-seeking vulnerabilities.

"We may predict that elevation in DAT-aAbs titres could be useful to screen for people with a given behavioural profile, likely to engage in 'risky business,' for instance. Imagine what avenues could be opened if the screening for DAT-aAbs would allow us to distinguish those whose immune issues go on to precipitate psychiatric illness from those who do not!"

References

1. Adriani W et al. Immunization with DAT fragments is associated with long-term striatal impairment, hyperactivity and reduced cognitive flexibility in mice. Behav Brain Funct. 2012;8: 54.

2. Giana G et al. Detection of auto-antibodies to DAT in the serum: interactions with DAT genotype and psycho-stimulant therapy for ADHD. J Neuroimmunol. 2015;278:212-22.