SEROtonIN TRANSPortER (SERT) BRAIN DENSITY AND NEUROBIOLOGICAL CLONINGER SUBTYPES MODEL: A LESSON BY HUMAN AUTORADIOGRAPHY STUDIES

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Abstract — Cloninger proposed a neurochemical model of alcoholism suggesting that type 2 alcoholics have serotoninergic deficits with intact dopaminergic system, whereas the type 1 alcoholics have defected dopaminergic system. The work by Storvik and colleagues recently published on Alcohol and Alcoholism shows some interesting differences on the SERT brain density between the type I and type II alcoholic subtypes. Critically, these findings on different serotonin role in subtypes of alcohol-dependence revive the concept that alcohol addiction is a heterogeneous disorder associated with varying neurochemical abnormalities. Studies testing serotoninergic medications in alcohol-dependent patients classified according to subtypes have shown interesting findings. Accordingly, the identification and standardization of alcoholic subtypes could be useful in guiding research on treatment. New developments in the neurobiological understanding of subtypes of alcoholic patients, could led to get the basis for a more personalized pharmacological therapy.

In 1981 Cloninger, Bohman and Sigvardsson (Cloninger et al., 1981) identified two alcoholic subtypes and named them type 1 and type 2. Cloninger typologies overlap to some extent with type A/B subtypes of Babor et al. (1992). In particular both typologies share the early (Cloninger 2 and Babor B) or late (Cloninger 1 and Babor A) onset. Type 1 alcoholics manifest fewer associated childhood antisocial behaviors; type 2 alcoholics have persistent antisocial behaviors and a high familial risk for alcoholism. Cloninger and colleagues (1981) suggested that type 2 alcoholics have a strong genetic diathesis while type 1 alcoholics are influenced more strongly by social milieu factors. The Cloninger type 2 alcoholics are almost exclusively men, a feature in line with the innate male aggression-seeking behavior. Cloninger proposed a neurochemical model of alcoholism suggesting that type 2 alcoholics have serotoninergic deficits with intact dopaminergic system, whereas the type 1 alcoholics have defective dopaminergic systems (Cloninger, 1995).

It has been suggested that different patients may have different profiles of craving, which can hold specific neurobiological pathways (Addolorato et al., 2005). Different anti-craving drugs could preferentially act on different neurobiological mechanisms and accordingly certain subpopulations of alcohol-dependent people could better benefit by different pharmacological medications (Addolorato et al., 2005). Consequently, the identification and standardization of alcoholic subtypes could be useful in guiding research on treatment. This is the case of medications acting on the 5-HT system. In fact, studies testing serotoninergic medications in alcohol-dependent patients classified according to subtypes have shown interesting findings. In particular, it has been suggested that ondansetron could be useful in early-onset patients (Pettinati et al., 2000) whereas sertraline in late-onset patients (Pettinati et al., 2000). Conversely, fluoxetine appeared to reduce the beneficial effects of cognitive–behavioral therapy in type B (early onset) alcoholics (Kranzler et al., 1996). Taking all these studies together, they have suggested “new vistas” (Kranzler, 2000) on the treatment of alcoholism, getting over the “scientific frustration” (Johnson, 2000) due to previous trials showing the lack of efficacy of serotoninergic drugs in alcohol-dependent patients (Swift, 1999). After these mentioned trials, serotonin reuptake inhibitors and ondansetron have been suggested as promising medications in certain subgroups of alcoholics (Anton and Swift, 2003). Finally, a recent European study has suggested that also naltrexone seems more useful in type 2 alcoholic patients (Kiefer et al., 2007). Taking into account the Cloninger neurochemical model (1995) the results by Kiefer and colleagues could be in line with the animal data demonstrating that the µ-opioid receptors are able to modulate the 5-HT system in the dorsal raphe nucleus and nucleus accumbens (Tao and Auerbach, 2002).

Other subtypes classifications have also given interesting data in terms of pharmacological treatment of alcoholism. In particular, the Lesch typology classification (Lesch et al., 1990) has shown its utility to differentiate the pharmacological response of alcoholic patients, particularly those treated by the glutamate modulator acamprosate (Lesch et al., 2001). Interestingly, Walter and colleagues (Walter et al., 2006) have recently shown that glutamic acid levels did not differ in the two Cloninger typologies whereas different values were found in different Lesch typologies. Accordingly there was no significant association between Cloninger and Lesch typologies in the alcoholic patients studied (Walter et al., 2006). In other words, different subtypes classifications seem to reflect different neurobiological systems. In particular, Cloninger typologies – mostly the type 2 – seem to be strongly related to the 5-HT system. Furthermore, it has been suggested that alcoholics with a biological disease predisposition do not have a simple serotonin deficiency but the abnormality may be related more to the regulation of serotoninergic function (Johnson, 2000). On this point, the serotonin transporter (SERT) seems to have a key role. In fact, animal studies performed both in...
mice (Boyce-Rustay et al., 2006) and in nonhumans primates (Heinz et al., 1998) support an important role for the SERT in regulating serotonergic neurotransmission in alcohol addiction. Several human studies have investigated the role of the SERT polymorphism 5-HTTLPR in alcohol dependence (Feinn et al., 2005) and in particular the role of the SERT genotype has been underlined in adolescents (Hinckers et al., 2006). Furthermore, in vivo human studies using imaging techniques have also suggested a role of SERT in alcoholic patients (Szabo et al., 2004).

In recent years the post-mortem human studies performed by Dr. Markus Storvik and colleagues (Storvik et al., 2006) have focused on the different roles of the SERT in subtypes of alcoholic patients, specifically the Cloninger typologies. The last study (Storvik et al., 2008) represents a further evidence by this research lab on this topic. The limits of their studies—small number of subjects analyzed and selection of single set of subjects from the population—are amply filled up by the interesting findings. Authors’ lab previously reported decreased SERT density in the perigenual anterior cingulate cortex (PACC) (Mantere et al., 2002), in the dorsal striatum (Storvik et al., 2006) and in the dorsal level of the amygdala in the alcoholics (Storvik et al., 2007). Interestingly, they found a statistically significant positive correlation of SERT binding between the body of the caudate and the upper level of the PACC only in the type 1 alcoholics (Storvik et al., 2006). Moreover, a lower SERT binding in the amygdala was found in type 2 with respect to controls (Storvik et al., 2007). In this study Storvik and colleagues’ (2008) aim was to evaluate the SERT binding densities in the PVN of alcoholics. In order to further evaluate the serotonergic system in the brain areas that are important for the regulation of the impulsive aggression, the SERT binding between the PVN and the limbic areas were compared in the alcoholic groups and controls to determine if serotonergic alterations in these cerebral areas are correlated with each other in a similar or different way in type 1 and type 2 alcoholics. Furthermore, Storvik and colleagues used correlation analysis to compare the data of the present study on the SERT binding in PVN with their previously published data from the amygdala (Storvik et al., 2007), dorsal striatum (Storvik et al., 2006) and from the prefrontal cortical regions (Mantere et al., 2002).

The results by Storvik et al. (2008) are inspiring and of interest since they strongly support the Cloninger model for the neurobiological typology of alcoholics. In the type 2 alcoholics, the trend towards decreased SERT density together with the lack of decline with age suggest that the SERT may be already decreased in the PVN in the early adulthood. The trend towards decrease of SERT density in PVN is in line with those reported from other brain areas (Mantere et al., 2002; Storvik et al., 2006) in the same subjects. The observed significant positive correlation between SERT binding densities in the dorsal and ventral amygdala and in PVN supports the hypothesis that serotonergic system is defective in both of these regions in the type 2 alcoholics. Since in the type 1 alcoholics the SERT seems to decrease only in the amygdala (Storvik et al., 2007) and not in the PVN, this last feature supports the typical antisocial and aggressive behavior of the type 2 alcoholics. A reduced SERT density in the raphe nuclei associated with an early alcoholism onset in violent offenders was already shown by the same Finnish lab in an in vivo study (Tiitonen et al., 1997). The serotonergic defect in both violent patients and in alcoholics was subsequently confirmed in an in vivo U.S. study; the association between pathological aggressive behavior and a reduction in SERT availability mainly in the anterior cingulate cortex was reported (Frankle et al., 2005). However, a more recent in vivo U.S. imaging study failed to show similar findings (Brown et al., 2007). As speculated by Storvik and colleagues (2007), these contrasting data could be due to the competition between the used [(11)C]DASB ligand and the endogenous serotonin. However, also other features could influence these different results. First of all, the difficulty to compare in vivo imaging investigations and post-mortem studies. Furthermore, rat models have shown that alcohol is able to influence the neuroplasticity of serotonergic neurons also inducing excessive cell death via oxidative stress (Goodlett et al., 2005). On this point, it should be underlined that ethanol per se seems to be able to increase oxidative parameters in humans, also in a moderate amount (Addolorato et al., 2008).

Further larger studies investigating the neurobiological pattern of subtypes of alcoholics in different populations are needed to clarify these contrasting data.

In summary, the autoradiography findings by Storvik and colleagues suggest that the correlations between SERT binding and age and between the SERT binding in PVN and amygdala are different between the type 1 and type 2 alcohol subtypes. According to the hypothetical genetic diathesis, the type 2 alcoholics seem to have a SERT decrease already present in early age. Conversely, in the type 1 alcoholics the serotonergic alterations may be secondary and possibly reflecting the alterations in the dopaminergic system. In a previous study Tupala and colleagues (Tupala et al., 2003) showed that the dopamine transporter (DAT) density declined significantly with age in healthy controls and type 2 alcoholics while no correlation between age and DAT density was found in the type 1 alcoholics. In this led to speculate that a pre-existing dopaminergic deficit is peculiar only in type 1 alcoholics. In this study by Storvik et al. (2008) and the previous study by Tupala et al. (2003) represent the “two sides of the coin”. Although more and more research is needed to understand individual vulnerability to addiction and the related “dark side” of drug dependence (Koob and Le Moal, 2005), the findings by the Finnish lab are surely inspiring. Critically, these findings on different serotonergic role in subtypes of alcohol-dependence revive the concept that alcohol addiction is a heterogeneous disorder associated with varying neurochemical abnormalities. From a practical point of view, these features highlight the need for a transformation of how alcoholism treatment is viewed by clinicians (Kenna, McGearry and Swift, 2004). New developments in the neurobiological understanding of subtypes of alcoholic patients, could lead to get the basis for a more personalized pharmacological therapy.

REFERENCES


