Integration of neuronal and glial signalling by pyramidal cells of the rat prefrontal cortex; control of cognitive functions and addictive behaviour by purinergic mechanisms

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The medial prefrontal cortex (PFC) is thought to be the highest order association area in the mammalian cortex which is involved in cognitive functions. Especially, layer V pyramidal cells integrating afferent innervations from dopaminergic cell groups in the ventral tegmental area, glutamatergic inputs from the thalamus and neighbouring PFC pyramical cells, as well as GABAergic inputs from local interneurons are crucial for processing short-term working memory. These neurons are endowed with the NMDA- and AMPA-type excitatory amino acid receptors, described to be involved in the regulation of synaptic plasticity, the apparent basis of elementary learning processes. NMDA receptor currents were in fact regulated on the one hand by dopamine D1 receptors and on the other hand by ATP-sensitive receptors of the P2Y-type. P2Y4 receptors acted indirectly to potentiate NMDA receptor-currents by releasing vesicular glutamate from astrocytes, or attenuated these currents directly by stimulating P2Y1 receptors located at the PFC cells themselves. Long-term depression (LTD) induced in PFC pyramidal neurons could be blocked by P2Y1 receptors in a manner not depending on NMDA receptors but targeting voltage-sensitive dendritic Ca^{2+} channels. *In vivo* data also support the notion that P2Y1 receptors participate in the regulation of cognitive processes and addiction. For example, in a spatial delayed win-shift task, P2Y1 receptor-activation has been shown to deteriorate not the primary storage of information but its processing during and after a delay. Further, it is widely accepted that behavioural sensitization in animals provides a model for the intensification of drug craving believed to underlie addiction in humans. In fact, sensitization to amphetamine was interrupted by the blockade of P2Y1 receptors in the mesocortico-limbic dopaminergic system.

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PURINERGIC SIGNALLING

ATP is released from healthy cells and reaches the extracellular space as a transmitter, co-transmitter or signalling molecule released from neurons or glial cells (Burnstock, 2004; Illes and Ribeiro, 2004). However, pathological concentrations of ATP may arise in the neighbourhood of injured or dying cells, because of a spontaneous efflux of the purine via the damaged plasma membrane which is no longer a barrier for the extremely high intracellular ATP levels to pour out (Köles et al., 2005; Burnstock et al., 2011). ATP acts at two types of membrane receptors called P2X (ligand-gated cationic channels) and P2Y (G protein-coupled receptors) (Abbracchio and Burnstock, 1994). Both of them are further classified into several subtypes (P2X1-7; P2Y1,2,4,6,11,12,13,14) occurring in various mammalian cell types (Khakh et al., 2001; Abbracchio et al., 2006). Furthermore, a complex family of ectoenzymes rapidly metabolizes extracellular nucleotides producing either inactive degradation products or active metabolites with sometimes altered purinoceptor selectivity (Zimmermann, 2000). While ATP/ADP stimulates the P2 receptors, adenosine activates its own receptors of the P1 class. Since P2 and P1 receptors are often

functionally antagonistic, the breakdown of ATP not only terminates purinergic signalling but brings new players with different properties into the game as well. Eventually, external ATP may also fulfil a regulatory function as a phosphate donor and phosphorylate membrane constituents thereby modulating their properties (Wirkner et al., 2005).

INTERACTION BETWEEN THE DOPAMINERGIC AND GLUTAMATERGIC SYSTEMS IN THE PREFRONTAL CORTEX

The medial prefrontal cortex (PFC) is thought to be the highest order association area in the mammalian cortex which is involved in working memory and decision making (Goldman-Rakic, 1995) as well as in the pathophysiology of schizophrenia and addiction (Grossberg, 2000) in both primates and rodents. It has been reported that layer V pyramidal neurons play a key role in the network activity of the PFC (Gulledge and Stuart, 2003) and are crucial for processing short-term working memory (Goldman-Rakic et al., 1989). Pyramidal neurones of the PFC are known to synapse in the VTA onto dopamine neurones that project back to the PFC but not onto such that project to the nucleus accumbens (Carr and Sesack, 2000). Further, PFC afferents control mesoaccumbal projection neurones by an indirect pathway involving neurones in the pedunculo pontine tegmentum and the laterodorsal tegmentum (LDT) (Del Arco and Mora, 2008). PFC neurons in turn receive afferent innervations from dopaminergic cell groups localized in the ventral tegmental area (Brozoski et al., 1979). The glutamatergic input originates from the mediodorsal nucleus of the thalamus and from neighbouring PFC pyramidal cells interconnected with each other (Groenewegen, 1988).

Dopamine may affect pyramidal neurons primarily through D1 receptor-mediated immediate excitability changes (Gulledge and Jaffe, 2001; Dong and White, 2003) or through an increased synaptic input from GABAergic interneurons (Seamans et al., 2001). PFC pyramidal neurons express all five subtypes of dopamine receptor mRNA (Lidow et al., 1998) as well as mRNA for the NMDA type excitatory amino acid (EAA) receptor (Scherzer et al., 1998). In consequence, dopamine appears to facilitate glutamatergic transmission onto PFC pyramidal neurons via a postsynaptic interaction between D1 and NMDA receptors (Cepeda et al., 1992; Seamans et al., 2001; Wirkner et al., 2004) both situated at the soma, dendritic shafts and synaptic spines of these neurons themselves (Goldman-Rakic et al., 1989). Whereas NMDA receptor-currents were potentiated by dopamine D1 but not D2 receptor-activation, AMPA receptor-currents were not altered under the same conditions (Wirkner et al., 2004). It is noteworthy that NMDA receptors are essential for normal information processing and for proper memory function (Nakanishi, 1992).

THE PURINERGIC SYSTEM IS A NEW PLAYER IN THE PREFRONTAL CORTEX; IN VITRO DATA

All previous experiments were performed in acutely prepared PFC slice preparations where the axonal projections of the mesocortico-limbic dopaminergic neurons located in the ventral tegmentum and terminating at the PFC pyramidal neurons were transected. To circumvent this complication we co-cultured individual brain slices of the ventral tegmentum/substantia nigra (VTA/SN complex) with those of the PFC (Franke et al., 2003b; Heine et al., 2007). After 10-28 days of culturing fibre bridges were established connecting the VTA/SN with the PFC. These fibre bridges functionally connect the two areas of the brain as proven by recording the orchestrated synaptic activity by means of a multielectrode array system (Dossi et al., 2012). Moreover, electrical stimulation in the VTA/SN induced glutamatergic EPSCs in the PFC. In contrast to previous results, D1 receptor agonists enhanced the NMDA component of the EPSC and inhibited its AMPA component – both isolated pharmacologically by the respective EAA antagonist. At the moment it is difficult to explain this inconsistency between the results obtained at acute PFC slices and organotypic cultures of the VTA/SN-PFC. However, one of the reasons may be that the dopaminergic agonists/antagonist flushed only the dopaminergic terminals and the innervated pyramidal neurons in the one case, whereas in the other case the cell bodies of the dopaminergic neurons are also incubated with the dopaminergic ligands.

The co-release of ATP has been repeatedly demonstrated from postganglionic sympathetic neurons in the periphery (von Kügelgen and Starke, 1991) and from locus coeruleus neurons of the central nervous system (CNS) (Poelchen et al., 2001). P2X receptors mediate a fraction of excitatory postsynaptic currents (EPSCs) of rat pyramidal neurons in the hippocampal CA1 layer (Pankratov et al., 2002) and layer II/III of the somatosensory cortex (Pankratov et al., 2002). P2Y receptors were shown to positively interact with NMDA receptors situated at PFC layer V pyramidal neurons (Wirkner et al., 2002) just as dopamine does (Wirkner et al., 2004). Thereby, the possible co-

transmitters dopamine and ATP (Krügel et al., 2001b) may shape in an equal and possibly additive fashion the glutamatergic excitation in the prelimbic area.

A wealth of data indicate that astrocytes are an integral element of the circuitry for synaptic plasticity (Araque et al., 2001). In addition to the neuronal release of EAAs, glutamate may be secreted from astrocytes not only (1) by exocytotic processes but also (2) by connexin hemichannels, providing a substrate for gap junction formation, (3) by glutamate transporters operating in the reverse mode, and (4) by a subtype of P2X receptors (P2X7), establishing a link between the release of ATP and glutamate (Illes and Ribeiro, 2004). In consequence, astrocytic glutamate is a possible factor modulating excitatory neurotransmission in neuronal networks (Nedergaard et al., 2002; Newman, 2003). ATP secretion from astrocytes has been suggested to occur by four alternative pathways, such as an exocytotic vesicular release, ATP cassette proteins, connexin hemichannels, and osmolytic transporters linked to anion channels (Illes and Ribeiro, 2004).

In view of these data the findings of Wirkner et al. (2002) reporting a positive interaction between P2Y and NMDA receptors at PFC pyramidal neurons, were reinvestigated by the same group of researchers (Wirkner et al., 2007). It was suggested that ATP may act at astrocytic P2Y4 receptors to exocytotically release vesicular glutamate onto neighbouring neurons. This glutamate stimulates type I mGluRs that positively modulate NMDA receptors through the G_q/phospholipase C/inositol 1,4,5-trisphosphate/Ca^{2+}/calmodulin kinase II transduction pathway. This picture was further complicated by experiments finding differences between the effect of glutamate exocytotically released from astrocytes by P2Y4 receptors, and the effect of glutamate accumulating after the blockade of the astrocytic glutamate transporter EAAT2 (GLT-1) (Oliveira et al., 2008). The blockade of astrocytic glutamate uptake may lead to the stimulation of group II mGluRs, while the triggering of exocytotic glutamate release by P2Y4 receptors may cause activation of group I mGluRs, both situated postsynaptically at layer V PFC pyramidal cells. Either group of mGluRs may interact with NMDA receptors in a positive manner. Interestingly an exclusively neuronal modulatory interaction between P2Y1 and NMDA receptors was also described (Luthardt et al., 2003). In this case P2Y1 receptors appeared to interfere in a membrane delimited manner with the closely attached NMDA receptor-channels in the plasma membrane itself, since intracellular GDP-β-S, known to block the generation of $G_{\beta,\gamma}$ proteins transmitting such reactions, prevented the effect of P2Y1 receptor stimulation.

In hippocampal brain slices of rats ATP appeared to activate P2X7 receptors at astroglial cells causing the release of glutamate which in turn activated a tonic current in CA1 pyramidal neurons (Fellin et al., 2006). However, at least in the rat PFC, there was no indication for any effect of the preferential P2X7 receptor agonist dibenzoyl-ATP (Bz-ATP) on the amplitude of excitatory postsynaptic currents (EPSCs; recorded in layer V and evoked by electrical stimulation in layer I/II), other than a marked and DPCPX reversible decrease (Oliveira et al., 2011). It was suggested that this effect is due to the displacement of adenosine from its storage sites by Bz-adenosine generated from Bz-ATP by enzymatic degradation (for hippocampal mossy fibre-CA3 synapses see Kukley et al., 2004).

Long-term and bidirectional changes in synaptic strength are thought to provide a cellular basis for information storage in neuronal networks (Malenka and Bear, 2004). Studies investigating plasticity in layer V pyramidal cells of the PFC showed that tetanic stimulation of layer I/II induced either long-term potentiation (LTP) or long-term depression (LTD) which were both dependent on postsynaptic Ca^{2+} increases (Hirsch and Crepel, 1991; Hirsch and Crepel, 1992), see also Guzman et al., 2010). In subsequent studies, application of dopamine during tetanic stimulation induced a form of LTD (Law-Tho et al., 1995) that was found to be independent of NMDA receptors but required the activation of group I and II metabotropic glutamate receptors (mGluR) (Huang et al., 2004) and the mitogen-activated protein kinase (MAPK) pathway (Otani et al., 1999).

P2X receptors have been shown to play a role in the regulation of synaptic plasticity of central synapses resulting from their high Ca^{2+} permeability and capability to interact with other receptors (Pankratov et al., 2009). Moreover, previous studies revealed the presence of postsynaptic P2Y1 receptors on layer V pyramidal neurons in the PFC (see above). It has furthermore been shown that LTD in layer V pyramidal neurons of the PFC depend on the activation of mGluR1 and voltage-sensitive Ca^{2+} channels (Guzman et al., 2005; 2010). The stimulation of P2Y1 receptors reduced Ca^{2+} transients associated with postsynaptic voltage-sensitive Ca^{2+} channels on apical dendrites and spines of layer V pyramidal neurons. It was suggested that this is the likely mechanism by which P2Y1 receptors are able to modulate synaptic plasticity.

THE PURINERGIC SYSTEM AND COGNITIVE FUNCTIONS; IN VIVO DATA FOR THE PREFRONTAL CORTEX

One basic principle for sensitisation and drug abuse is reward- and withdrawal-related learning. The global term 'learning' refers to multiple physical changes of the structure of the CNS, thereby altering neuronal circuits involved in perceiving, performing, thinking and planning, and influencing future behavioural outcome by retrieving experiences or 'memories' (Kandel et al., 2000). While processes of learning and memory are under intensive investigation altogether, there are only few *in vivo* studies on the function of P2 receptors interacting with cognitive abilities, in particular such focussing on purinergic mechanisms in the medial PFC.

An indirect, albeit important, *in vivo* confirmation of the role of ATP and ADP in cognitive behaviour initially came from studies at the hippocampus, where activities of the ATP-diphosphohydrolase and the 5'-nucleotidase were found to be decreased in rats after step-down inhibitory avoidance learning (Bonan et al., 1998; Rücker et al., 2004). This task triggers biochemical events in the hippocampus similar to LDP/LTP. Suramin, a broad spectrum P2 receptor antagonist and blocker of NMDA-receptors applied immediately post-training has been shown to impair inhibitory avoidance retention (Bonan et al., 1999) and also to interfere with responses to conditioned fear stimuli (Zou et al., 1998). Because in the latter approach D,L-2-amino-5-phosphonovaleric acid (APV) did not block the expression of fear conditioning, it was suggested that the effects of suramin were mediated by P2 receptors (Kim et al., 1991).

In a single trial bead discrimination test with young chicken, Cronin et al. (2011) observed two time points sensitive for memory retention after intracranial infusion of suramin and the more selective P2 receptor antagonist PPADS until 2.5 minutes post-training and about 30 minutes afterwards (Cronin et al., 2011). These two periods of effective administration times suggested an impact of P2 receptor stimulation on the early short-term and the intermediate-term memory stages (Gibbs and Ng, 1977).

It is generally believed that any trial-specific information maintained for minutes or hours is supported by the hippocampus and its projections to the PFC. On the other hand, the role of the PFC is not only to maintain information in working memory over a period of seconds but also to learn associations between context, locations and events and thereby to control executive functions, such as planning, organization, decision making, and adaptation (Euston et al., 2012; Chudasama, 2011). Some of the most compelling evidence for the fact that the PFC is involved in the control of information required to prospectively organize the ongoing action was provided by lesion studies in which the performance of rats gets worse when sets of interfering events were presented during a delay phase within a memory task but not by the delay itself (Gisquet-Verrier and Delatour, 2006).

Own data obtained from rats in a spatial delayed win-shift task have shown after introduction of a first delay that the performance was impaired independently of stimulation of prefrontal P2Y1 receptors by the selective agonist MRS2365 (Burnstock et al., 2011). When trials with the delay were repeated at subsequent days, both MRS2365-treated animals and their controls were able to acquire the delayed task finally. However, each pre-trial infusion of MRS2365 caused more errors in the phase after the delay than that of vehicle. This may suggest that prefrontal P2Y1 receptors are not primarily involved in the 'short-term' storage of information *per se* but in its processing during and after the delay ('recall'). It can be speculated that the activation of P2Y1 receptors enhances the recognition and processing of stimuli negligible for the ongoing task. This idea is supported by data generated in a social discrimination setting, where an adult animal has to distinguish between a familiar and unfamiliar juvenile (Koch et al., 2010). MRS2365 applied into the rat prefrontal cortex immediately prior to the test, deteriorated the naturally preferred investigation of the unfamiliar juvenile. As the overall time of inspection of both animals was unchanged, disturbed prefrontal information processing resulting in a lower capacity to focus on the unfamiliar juvenile by activation of P2Y1 receptors can be assumed. These attentional deficits mediated by prefrontal ATP are in agreement with data showing that the rodent PFC is indispensible to filter incoming relevant from irrelevant stimuli (Schneider and Koch, 2005). Own preliminary data from the PFC and the motor cortex of rats (Koch et al., 2010; Franke et al., 2004) confirmed the presence of P2Y1 receptors on neurones and astrocytes in the respective cortical areas. Functional neuroimaging and clinical data revealed that cognitive alterations in attention, behavioural inhibition, learning and memory found in addictive disorders are strongly related to dysfunctions of the PFC, so the involvement of P2 receptors is very likely (for review see Goldstein and Volkow, 2011).

In a very recent study on mice which investigated another behavioural phenomenon commonly accompanied by cognitive deficits, stress-induced depressive-like behaviour, the stimulation of endogenous ATP release from astrocytes induced antidepressive-like effects, obviously mediated by P2X2 receptors located in the PFC. The infusion of ATP and ATP-γ-S, which is a not hydrolysable structural analogue, into the PFC but not into the hippocampus could reverse the stress-induced behavioural changes (Cao et al., 2013).

THE PURINERGIC SYSTEM AND ADDICTION; IN VIVO DATA FOR THE PREFRONTAL CORTEX

Repeated exposure to many drugs of abuse results in a progressive and enduring enhancement of the motor stimulant effect elicited by a subsequent drug challenge (Wolf, 1998; Vanderschuren and Kalivas, 2000). This so called behavioural sensitization provides an animal model for the intensification of drug craving believed to underlie addiction in humans. Mechanistic similarities between sensitization and other forms of neuronal plasticity were first suggested on the basis of the ability of NMDA receptor antagonists to prevent the development of sensitization (Karler et al., 1989).

Amphetamine-like drugs release dopamine into the PFC by the activation of dopaminergic cell bodies in the NAc; subsequently glutamatergic projections between the PFC and amygdala are stimulated, as well as glutamatergic outputs to the NAc and ventral tegmental area (Steketee, 2003; Kalivas, 2007). These latter projections play an apparently critical role in initiating drug seeking or craving. Thus, a dramatic increase in the density of dendritic spines of the NAc is elicited, accompanied by the enhancement of the insertion of AMPA receptors into the membrane of medium spiny neurons of the NAc associated with an increase in electrophysiological sensitivity to AMPA receptor stimulation (this mechanism is identical with that supposed to be a basis for LTP or LTD [Wolf et al., 2003]). Similar changes also occur after the application of NMDA receptor antagonists which disturb the balance between NMDA and AMPA receptor-mediated functions.

Application of the non-selective P2 receptor agonist 2-methylthio ATP (2-MeSATP) into the NAc of rats raises the extracellular level of dopamine (Krügel et al., 1999), accompanied with enhanced locomotion (Kittner et al., 2000). The repetitive intraperitoneal (i.p.) injection of amphetamine for 5 successive days with a subsequent drug-free interval of 5 days led to an enhanced locomotion in comparison with the response after the first amphetamine application (Franke et al., 2003a; Kittner et al., 2001). Intracerebroventricular (i.c.v.) pre-treatment with PPADS prior to each amphetamine administration prevented the development of sensitization. Hence it was suggested that the activation of P2 (probably P2Y1) receptors by endogenous ATP was an intermediary step in the sensitization process to amphetamine. This is supported by data, where repetitive stimulation of ventral tegmental dopaminergic neurons endowed with P2Y1 receptors by 2-MeSATP induced a behavioural sensitization to a single amphetamine challenge (Krügel et al., 2001a).

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A prefrontális kéreg piramissejtjeinek integráló szerepe a neuronális és glia eredetű információk feldolgozásában, patkányban; a kognitív funkciók és az addiktív viselkedés purinerg mechanizmusokkal történő szabályozása

A mediális prefrontális kérget (PFC) tekintik az emlős agykéreg legmagasabb rendű asszociációs területének, amely a kognitív funkciókban játszik szerepet. E terület 5. rétegének piramissejtjei kiemelkedő jelentőségűek a rövid távú munkamemória folyamatában. Általuk valósul meg a beérkező jelek integrációja, amely a ventrális tegmentális área dopaminerg sejtcsoportjaiból, a thalamus és a környező PFC piramissejtek glutamáterg valamint a helyi interneuronok GABAerg információiból származik. Ezeken a neuronokon megtalálhatók az NMDA és az AMPA típusú excitáros aminosav receptorok, amelyek szerepet játszanak az elemi tanulási folyamatok alapját képező szinaptikus plaszticitás szabályozásában. Az NMDA receptorok áramait egyrészt D1 dopamin receptorok, másrészt az ATP P2Y típusú receptorai szabályozzák. Utóbbi indirekt és direkt módon is megvalósul: a P2Y4 receptorok az asztrocitákból történő vezikuláris glutamát felszabadulás által fokozzák az NMDA receptorok áramait, míg a PFC neuronokon található P2Y1 receptorok stimulációja az NMDA áramok csökkenéséhez vezet. A PFC piramissejtjein kiváltott long-term depression (LTD, a szinaptikus hatékonyság hosszútávú csökkenése) P2Y1 receptorok aktiválásával blokkolható, amely hatás nem függ az NMDA receptoroktól, ezzel szemben a dendritek feszültségfüggő Ca^{2+} csatornái érintettek abban. *In vivo* adatok is alátámasztják azt a feltételezést, hogy a P2Y1 receptorok szerepet játszanak a kognitív folyamatok és az addikció szabályozásában. Például Delayed Spatial Win-Shift teszt esetében a P2Y1 receptorok aktiválása nem az elsődleges információtárolást rontja, hanem annak a folyamatát a késleltetés alatt és után. Általánosan elfogadott nézet, hogy az állatkísérletekben tapasztalt viselkedési szenzitizáció a humán addikció alapjául szolgáló drug craving (sóvárgás) felerősödésének a modellje. A P2Y1 receptorok blokádja a mezokortiko-limbikus dopaminerg rendszerben az amfetaminra történő szenzitizációt felfüggeszti.

Kulcsszavak: prefrontális kortex, dopamin, D1 receptorok, D2 receptorok, glutamát, NMDA receptorok, AMPA receptorok, ATP, P2X receptorok, P2Y receptorok